

PRESCRIBING INFORMATION

**PREMARIN[®] INTRAVENOUS
(Conjugated Estrogens for Injection, C.S.D.)**

25 mg CE/vial

ESTROGENIC HORMONES

©
**WYETH CANADA
MONTREAL, CANADA**

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TABLE OF CONTENTS

NAME OF DRUG	3
PHARMACOLOGIC CLASSIFICATION	3
ACTIONS AND CLINICAL PHARMACOLOGY	3
INDICATIONS AND CLINICAL USE.....	8
CONTRAINDICATIONS	8
WARNINGS	9
PRECAUTIONS	13
DRUG INTERACTIONS	14
ADVERSE REACTIONS.....	16
DOSAGE AND ADMINISTRATION	17
DIRECTIONS FOR STORAGE AND RECONSTITUTION	18
SYMPTOMS AND TREATMENT OF OVERDOSAGE	18
PHARMACEUTICAL INFORMATION.....	19
AVAILABILITY OF DOSAGE FORMS	19

NAME OF DRUG

PREMARIN® Intravenous

Conjugated Estrogens for Injection, C.S.D., 25 mg/vial

Warning

The Women's Health Initiative (WHI) study results indicated increased risk of myocardial infarction (MI), stroke, invasive breast cancer, pulmonary emboli and deep venous thrombosis in postmenopausal women receiving treatment with oral combined conjugated estrogens and medroxyprogesterone acetate compared to those receiving placebo tablets. Other combinations and dosage forms of estrogens and progestins were not studied. In the absence of comparable data, these risks should be assumed to be similar. Therefore, the following should be considered when estrogens and progestins are prescribed:

- Estrogens with or without progestins should not be prescribed for primary or secondary prevention of cardiovascular diseases.
- Estrogens with or without progestins should be prescribed at **the lowest effective dose** for the approved indication.
- Estrogens with or without progestins should be prescribed for **the shortest period** possible for the recognized indication.

PHARMACOLOGIC CLASSIFICATION

Estrogenic Hormones.

ACTIONS AND CLINICAL PHARMACOLOGY

By a direct action, endogenous estrogens cause growth and development of the uterus, fallopian tubes, and vagina. With other hormones, such as pituitary hormones and progesterone, they cause enlargement of the breasts through promotion of ductal growth, stromal development, and the accretion of fat. Estrogens are intricately involved with other hormones, especially progesterone, in the processes of the ovulatory menstrual cycle and pregnancy, and affect the release of pituitary gonadotropins. Indirectly, they also contribute to the shaping of the skeleton, maintenance of tone and elasticity through the increase of collagen production in the supportive tissues of the heart, skin and urogenital structures, changes in the epiphyses of the long bones that allow for the pubertal growth spurt and its termination, growth of axillary and pubic hair and pigmentation of the nipples and genital tissues. Decline of ovarian estrogenic and progestogenic activity at the end of the menstrual cycle can result in menstruation, although the cessation of progesterone secretion is the most important factor in the mature ovulatory cycle. However, in the preovulatory or nonovulatory cycle, estrogen is the primary determinant in the onset of menstruation.

Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is substantially more potent than estrone or estriol at the receptor level. The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70 to 500 micrograms 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 estrogens in postmenopausal women.

Circulating estrogens modulate pituitary gonadotropins, luteinizing hormone (LH) and follicle stimulating hormone (FSH) through a negative feedback mechanism. Estrogen therapy acts to reduce elevated levels of these hormones seen in postmenopausal women.

Estrogen drug products act by regulating the transcription of a limited number of genes. They may act directly at the cell's surface via non "estrogen receptor" mechanism or directly with the estrogen receptor inside the cell. Estrogens diffuse through cell membranes, distribute themselves throughout the cell, and bind to and activate the nuclear estrogen receptor, a DNA-binding protein which is found in estrogen-responsive tissues. The activated estrogen receptor binds to specific DNA sequences, or hormone-response elements, which enhance the transcription of adjacent genes and in turn lead to the observed effects. Estrogen receptors have been identified in the wall of blood vessels, in tissues of the reproductive tract, breast, pituitary, hypothalamus, liver, and bone of women.

Conjugated estrogens are soluble in water and are well absorbed through the skin, mucous membranes, and gastrointestinal tract after release from the drug formulation. Some estrogens are excreted in bile; however, they are reabsorbed from the intestine and returned to the liver through the portal venous system. Water-soluble estrogen conjugates are strongly acidic and are ionized in body fluids, which favours excretion through the kidneys since tubular reabsorption is minimal.

When applied for a local action, absorption is usually sufficient to cause systemic effects. When conjugated with aryl and alkyl groups for parenteral administration, the rate of absorption of oily preparations is slowed with a prolonged duration of action, such that a single intramuscular injection of estradiol valerate or estradiol cypionate is absorbed over several weeks.

Administered estrogens and their esters are handled within the body essentially the same way as the endogenous hormones.

Women's Health Initiative Study

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 (CEE) [0.625 mg daily] alone or in combination with medroxyprogesterone acetate (MPA) [0.625 mg/2.5 mg daily] compared to placebo. The primary endpoint was the incidence of coronary heart disease (CHD), i.e. non-fatal myocardial infarction (MI), silent MI and coronary death. The primary safety endpoint was incidence of invasive breast cancer. The substudy did not evaluate the effects of hormone therapy on menopausal symptoms.

The oral 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 the table below.

In the oral 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), (RR 0.64, 95% nCI 0.44-0.93), and (RR 0.71, 95% nCI 0.64-0.80), respectively. The estrogen-alone substudy did not report a statistically significant effect on death due to other causes (RR 1.08, 95% nCI 0.88-1.32). There was no 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 -1: Relative and Absolute Risk Seen in the Oral Estrogen-Alone Substudy of WHI

Event	Relative Risk Oral ET vs Placebo (95% nCI ^a)	Absolute risk per 10,000 Person-years	
		ERT (n = 5,310)	Placebo (n = 5,429)
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	1.37 (1.09-1.73)	45	33
Deep vein thrombosis ^b	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	0.65 (0.45-0.94)	12	19
Vertebral fractures ^c	0.64 (0.44-0.93)	11	18
Total fractures ^c	0.71 (0.64-0.80)	144	197

Table -1: Relative and Absolute Risk Seen in the Oral Estrogen-Alone Substudy of WHI

Event	Relative Risk Oral ET vs Placebo (95% nCI ^a)	Absolute risk per 10,000 Person-years	
		ERT (n = 5,310)	Placebo (n = 5,429)
Death due to other causes ^{c,d}	1.08 (0.88-1.32)	53	50
Overall mortality ^c	1.04 (0.88-1.22)	81	78

^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 7.1 years.

^d All deaths, except from breast or colorectal cancer, definite/probable CHD, PE, or cerebrovascular disease.

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 CEE alone compared with placebo.

The oral 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, at that time, exceeded the specified benefits (such as the reduction of colorectal cancer and hip fracture). Results of the estrogen-plus-progestin substudy of WHI, which included 16,608 women (average age of 63 years, range 50 to 79) after an average follow-up of 5.6 years are presented in the table below. These results reflect centrally adjudicated data after an average follow-up of 5.6 years.

In the WHI oral estrogen-plus-progestin substudy, an increase in CHD risk was associated with combined hormone therapy (RR 1.24, 95% nCI 1.00-1.54). This was most apparent in the first year of the study (RR 1.81, 95% nCI 1.09-3.01). The RR of invasive breast cancer (RR 1.24, 95% nCI 1.01-1.54) was increased in women on combined hormone therapy. The substudy also reported a statistically significant increased RR of overall stroke (RR 1.31, 95% nCI 1.02-1.68), ischemic stroke (RR 1.44, 95% nCI 1.09-1.90), DVT (RR 1.95, 95% nCI 1.43-2.67), and PE (RR 2.13, 95% nCI 1.45-3.11). Estrogen plus progestin was found to increase bone mineral density vs. placebo (3.7% vs. 0.14%, $P < 0.001$) after three years. A statistically significant reduced RR of hip (RR 0.67, 95% nCI 0.47-0.96), vertebral (RR 0.65, 95% nCI 0.46-0.92), lower arm/wrist (RR 0.71, 95% nCI 0.59-0.85), and total fractures (RR 0.76, 95% nCI 0.69-0.83) was associated with estrogen plus progestin use.

Oral estrogen plus progestin use was associated with a statistically significant decreased risk of invasive colorectal cancer (RR 0.56, 95% nCI 0.38-0.81) although when colorectal cancers were diagnosed in combined hormone users, they were more advanced. Additional analyses showed no statistically significant differences in relative risk of endometrial (RR 0.81, 95% nCI 0.48-1.36) or cervical (RR 1.44, 95% nCI 0.47-4.42) cancers in patients on combined hormone replacement therapy vs. placebo. After an average of 5.2 years of follow-up, the estrogen-plus-progestin substudy did not report a statistically significant effect on death due to other causes

(RR 0.92, 95% nCI 0.74-1.14), and there was no effect on overall mortality risk (RR 0.98, 95% nCI 0.82-1.18). These confidence intervals are unadjusted for multiple looks and multiple comparisons.

Table -2: Relative and Absolute Risk Seen in the Oral Estrogen Plus Progestin Subset of WHI at an Average of 5.6 Years^a

Event	Relative Risk HT [†] vs. Placebo (95% nCI ^b)	Absolute risk per 10,000 Person-years	
		HRT (n = 8506)	Placebo (n = 8102)
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.

[†] conjugated estrogen tablets, 0.625 mg, and medroxyprogesterone acetate tablets, 2.5 mg.

PHARMACOKINETICS

Distribution

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

Metabolism

Metabolic conversion of estrogens occurs primarily in the liver (first pass effect), but also at local target tissue sites. Complex metabolic processes result in a dynamic equilibrium of circulating conjugated and unconjugated estrogenic forms which are continually interconverted, especially between estrone and estradiol and between esterified and non-esterified forms.

Estrogen drug products administered by non-oral routes while not subject to true “first-pass” metabolism, do undergo significant hepatic uptake, metabolism, and enterohepatic recycling. Metabolism and inactivation occur primarily in the liver. Some estrogens are excreted into the bile; however, they are re-absorbed from the intestine and returned to the liver through the portal venous system. Water-soluble estrogen conjugates are strongly acidic and are ionized in body fluids, which favour excretion through the kidneys since tubular re-absorption is minimal.

Excretion

A certain proportion of the estrogen is excreted into the bile, then reabsorbed from the intestine and returned to the liver through the portal venous system. During this enterohepatic recirculation, estrogens are desulfated and resulfated and undergo degradation through conversion to less active estrogens (estriol and other estrogens), oxidation to nonestrogenic substances (catecholestrogens, which interact with catecholamine metabolism, especially in the central nervous system), and conjugation with glucuronic acids (which are then rapidly excreted in the urine).

INDICATIONS AND CLINICAL USE

For abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology.

CONTRAINDICATIONS

Estrogens should not be used in women with any of the following conditions:

- Liver dysfunction or disease as long as liver function tests have failed to return to normal.
- Known, suspected, or past history of breast cancer.
- Known or suspected estrogen-dependent neoplasia (e.g., endometrial cancer)
- Endometrial hyperplasia
- Known or suspected pregnancy (see Warnings: Effects during pregnancy).

- Undiagnosed abnormal genital bleeding.
- Active or past history of confirmed venous thromboembolism (such as deep venous thrombosis, or pulmonary embolism) or active thrombophlebitis.
- Active or past history of arterial thromboembolic disease (e.g. stroke, myocardial infarction, coronary heart disease).
- Partial or complete loss of vision due to ophthalmic vascular disease.
- **Premarin[®] Intravenous** should not be used in patients hypersensitive to any of the ingredients.

WARNINGS

See Boxed Warning.

Failure to control abnormal uterine bleeding or its unexpected recurrence is an indication for curettage.

Premarin[®] Intravenous is indicated for short-term use. However, warnings, precautions and adverse reactions associated with oral CEE treatment should be taken into account.

Estrogen Replacement Therapy (ERT) and Hormone Replacement Therapy (HRT) have been associated with increased risks of certain cancers and cardiovascular diseases. The use of unopposed estrogens in women with an intact uterus is associated with an increased risk of endometrial cancer.

Cardiovascular risk

ERT has been associated with an increased risk of stroke and deep venous thrombosis (DVT).

HRT has been associated with an increased risk of cardiovascular events such as myocardial infarction (MI), as well as stroke, venous thrombosis and pulmonary embolism (PE).

The physician should be aware of the possibility of thrombotic disorders (thrombophlebitis, retinal thrombosis, cerebral embolism, and pulmonary embolism) during estrogen replacement therapy and be alert to their earliest manifestations. Should any of these occur or be suspected, estrogen replacement therapy should be discontinued immediately.

Risk factors for cardiovascular disease (e.g. hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) should be managed appropriately.

a. Stroke

In the oral estrogen-alone substudy of the Women's Health Initiative (WHI) (see Actions and Clinical Pharmacology: Women's Health Initiative Study), a statistically significant increased risk of stroke was reported in women receiving estrogen alone compared to women receiving

placebo (45 vs. 33 per 10,000 person-years). The increase in risk was observed during year one and persisted.

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

b. Coronary heart disease

In the oral estrogen-alone substudy of WHI (see Actions and Clinical Pharmacology: Women's Health Initiative Study), no overall effect on coronary heart disease (CHD) events (defined as non-fatal myocardial infarction (MI), silent MI or death due to CHD) was reported in women receiving estrogen-alone compared to placebo.

In the oral estrogen-plus-progestin substudy of WHI, no statistically significant increase of coronary heart disease (CHD) events was reported in women receiving the oral estrogen/progestin combination (CE 0.625 mg plus MPA 2.5 mg daily) compared to women receiving placebo (39 vs 33 per 10,000 person-years - 7 more cases). 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 post-menopausal 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 oral conjugated estrogens plus medroxyprogesterone acetate demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with oral conjugated estrogens plus medroxyprogesterone acetate did not reduce the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the hormone-treated group than in the placebo group in year one, but not during the subsequent years.

From the original HERS trial, 2,321 women 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 hormone-treated group in the HERS, the HERS II, and overall.

c. Venous thromboembolism

In the oral estrogen-alone substudy of WHI, the risk of VTE (deep venous thrombosis [DVT] and PE) was reported to be increased for women taking conjugated estrogens (30 vs 22 per 10,000 person-years), although only the increased risk of DVT reached statistical significance (23 vs 15 per 10,000 person-years). The increase in VTE risk was observed during the first two years.

In the oral estrogen-plus-progestin substudy of WHI (see Action and Clinical Pharmacology: Women's Health Initiative Study), a statistically significant 2-fold greater rate of VTE, was reported in women receiving the oral estrogen/progestin combination, compared to women receiving placebo (35 vs 17 per 10,000 person-years). Statistically significant increases in risk for both DVT (26 vs. 13 per 10,000 person-years) and PE (18 vs. 8 per 10,000 person-years) were also demonstrated. The increase in VTE risk was observed during the first year and persisted.

Generally recognized risk factors for VTE include a personal history, a family history (the occurrence of VTE in a direct relative or at a relatively early age may indicate genetic predisposition), systemic lupus erythematosus, and severe obesity (body mass index > 30 kg/m²). The risk of VTE also increases with age and smoking (see PRECAUTIONS).

Malignant neoplasms

a. Breast cancer

In some studies, use of oral ERT and HRT is associated with an increased risk of breast cancer.

In the oral estrogen-alone substudy of WHI, after an average of 7.1 years of follow-up, CEE (0.625 mg per day) was not associated with an increased risk of invasive breast cancer (RR 0.80, 95% nCI 0.62-1.04).

In the oral estrogen-plus-progestin substudy of WHI, after a mean follow-up of 5.6 years, the WHI substudy reported an increased risk of invasive breast cancer (RR 1.24, 95% nCI 1.01-1.54); invasive breast cancers were larger and diagnosed at a more advanced stage in the active therapy group compared to those in the placebo group. The absolute risk was 41 vs 33 cases per 10,000 person-years, for estrogen plus progestin compared with placebo, respectively. Metastatic disease was rare with no apparent difference between groups. Other prognostic factors such as histologic subtype, grade and hormone receptor status did not differ between groups.

Epidemiologic studies have reported an increased risk of breast cancer in women taking estrogens or estrogen/progestin combinations for HRT for several years. The excess risk increases with duration of use and seems to return to baseline in the course of about five years after stopping treatment. These studies also suggest that the risk of breast cancer is greater and becomes apparent earlier with estrogen/progestin combination therapy as compared to the use of estrogens alone.

Studies evaluating various HRT formulations did not show significant variation in the relative risk of breast cancer among formulations regardless of the estrogen/progestin components, doses, regimens, or route of administration.

According to data from epidemiologic studies, about 32 women in every 1000 women who never used HRT are expected to have breast cancer diagnosed between the ages of 50 and 65 years.

Among 1000 current or recent users of estrogen-only preparations, it is estimated that 5 and 10 years of use beginning at age 50 result in 1.5 (95% confidence interval (CI), 0-3) and 5 (95% CI, 3-7), respectively, additional breast cancers diagnosed by age 65 years. The corresponding numbers for those using estrogen/progestins combinations are 6 (95% CI, 5-7) and 19 (95% CI, 18-20), respectively.

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 health care provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled based on patient age, risk factors, and prior mammogram results.

b. Endometrial cancer

The use of unopposed estrogens in women with an intact uterus 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 1 year. The greatest risk appears associated with prolonged use, with increased risks of 15- to 24-fold for 5 to 10 years or more, and this risk has been shown to persist for at least 8 to 15 years after ERT is discontinued.

c. Ovarian cancer

In some epidemiologic studies, 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. The analysis of the WHI data suggested that oral estrogen plus progestin therapy may increase the risk of ovarian cancer.

Effects during pregnancy

Estrogens/progestins should not be used during pregnancy (see Contraindications).

Gallbladder disease

A 2- to 4-fold increase in the risk of surgically confirmed gallbladder disease requiring surgery has been reported in postmenopausal women receiving ERT/HRT.

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.

PRECAUTIONS

General precautions

Premarin[®] Intravenous is indicated for short-term use only. However, warnings, precautions and adverse reactions associated with oral CEE treatment should be taken into account.

When bleeding has stopped in cases of suspected uterine bleeding due to hormonal imbalance, a complete physical examination should be performed with special reference to pelvic and breast examinations. If the diagnosis is confirmed, appropriate measures should be taken to prevent a recurrence.

Hypertriglyceridemia

Women with pre-existing hypertriglyceridemia need special surveillance during estrogen replacement or hormone replacement therapy. 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 replacement therapy in this population.

Porphyria

Women with porphyria may need special surveillance during estrogen replacement or hormone replacement therapy since estrogens may exacerbate this condition.

Impaired liver function

Liver function tests should be done periodically in subjects who are suspected of having hepatic disease (see CONTRAINDICATIONS). Oral estrogens/progestins may be poorly metabolised in patients with impaired liver function. When liver or endocrine function tests are indicated, or surgical procedures are performed, the laboratory should be advised of the patient's therapy before specimens are forwarded. For information on endocrine and liver function tests, see section under **Laboratory Test Interactions**.

Past history of cholestatic jaundice

Caution is advised in patients with a history of estrogen- or pregnancy- related cholestatic jaundice. If cholestatic jaundice develops during treatment, medication should be discontinued, and appropriate investigations carried out.

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. Blood pressure should be monitored at regular intervals with HRT use. Elevation of blood pressure in previously normotensive or hypertensive patients should be investigated and HRT therapy may have to be discontinued.

Hypocalcemia

Estrogens should be used with caution in individuals with severe hypocalcemia.

Fluid retention

Because estrogens/progestins 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.

Exacerbation of other conditions

Estrogen/hormone replacement therapy may cause an exacerbation of asthma, epilepsy, migraine, diabetes mellitus with or without vascular involvement, systemic lupus erythematosus, and hepatic hemangiomas, and should be used with caution in women with these conditions.

Symptoms and physical findings associated with a previous diagnosis of endometriosis may reappear or be exacerbated with administration of ERT/HRT. Addition of a progestin should be considered in women who have undergone a hysterectomy but are known to have residual endometriosis, since malignant transformation after estrogen-only therapy has been reported.

Hypothyroidism

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

Pregnancy

Estrogens should not be used during pregnancy.

Lactation

Estrogens should not be used during lactation.

Pediatric Use

Premarin® Intravenous is not indicated in children.

DRUG INTERACTIONS

Estrogens may diminish the effectiveness of anticoagulants, antidiabetics and antihypertensive drugs.

Preparations affecting liver enzymes (e.g., barbiturates, hydantoins, carbamazepine, meprobamate, phenylbutazone or rifampicin) may interfere with the activity of estrogens.

Data from a drug-drug interaction study involving oral 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 17 β -estradiol, one of the components of conjugated estrogens, is metabolized partially by Cytochrome P450 3A4 (CYP3A4). Therefore, strong CYP3A4 inducers such as phenobarbital, phenytoin, carbamazepine, rifampicin and dexamethasone may reduce plasma concentrations of 17 β -estradiol. This may lead to a decreased effect and/or changes in the uterine bleeding profile. CYP3A4 inhibitors such as cimetidine, erythromycin, ketoconazole, clarithromycin, itraconazole, ritonavir, and grapefruit juice may increase plasma concentrations of 17 β -estradiol and may result in side effects.

It was found that some herbal products (e.g., St. John's wort) which are available as OTC products might affect metabolism, and, potentially, efficacy and safety of ERT/HRT products. Hot flashes and vaginal bleeding have been reported in patients taking estrogen/progestin and St. John's wort. St. John's wort may induce hepatic microsomal enzymes which theoretically may result in reduced efficacy of estrogen/progestin.

Physicians and other health care providers should be aware of other non-prescription products concomitantly used by the patient including herbal and natural products, obtained from the widely spread Health Stores.

Laboratory Test Interactions

The results of certain endocrine and liver function tests may be affected by estrogen-containing products:

- Accelerated prothrombin time, partial thromboplastin time, and increased norepinephrine-induced platelet aggregation time; increased platelet count; increased platelet factors II, VII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II, VII, X complex and beta-thromboglobulin; decreased levels of anti-factor Xa and antithrombin III, decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity;
- Increased thyroid-binding globulin (TBG) levels leading to increased circulating total thyroid hormone (T_4) as measured by protein-bound iodine (PBI), T_4 levels determined either by column or radioimmunoassay or T_3 levels by radioimmunoassay; free T_3 resin uptake is decreased, reflecting the elevated TBG; free T_4 and free T_3 concentrations are unaltered;
- Other binding proteins may be elevated in serum, i.e., corticosteroid binding globulin (CBG), sex hormone-binding globulin (SHBG), leading to increased circulating corticosteroids and sex steroids respectively. Free or biologically active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin);
- Impaired glucose tolerance. For this reason, diabetic patients should be carefully observed while receiving estrogen/progestin replacement therapy;

- Increased plasma HDL and HDL-2 subfraction concentrations, reduced LDL cholesterol concentration, increased triglyceride levels.

The results of the above laboratory tests may not be reliable unless therapy has been discontinued for two to four weeks. The pathologist should be informed that the patient is receiving ERT/HRT therapy when relevant specimens are submitted.

ADVERSE REACTIONS

The most serious adverse reactions associated with the use of estrogens are indicated under Warnings and Precautions.

The following adverse reactions have been reported with intravenous conjugated estrogens.

Reproductive system and breast disorders:

Very rare: Breast pain.

Gastrointestinal disorders:

Rare: ischemic colitis

Very rare: Nausea, vomiting, bloating, abdominal pain

Nervous system disorders:

Rare: possible growth potentiation of benign meningioma.

Very rare: Dizziness, headache, migraine, nervousness,

Vascular disorders:

Rare: Pulmonary embolism, venous thrombosis

Very rare: Superficial thrombophlebitis, hypotension, phlebitis (injection site).

General disorders and administration site conditions:

Rare: Injection site pain, injection site edema, edema.

Skin and subcutaneous tissue disorders:

Very rare: Rash.

Immune System Disorders:

Very rare: Urticaria, angioedema, anaphylactic/anaphylactoid reactions.

DOSAGE AND ADMINISTRATION

Abnormal uterine bleeding due to hormonal imbalance

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

Immediately start an estrogen-progestogen cyclic regimen such as conjugated estrogens 3.75 mg to 7.5 mg daily in divided doses (as tablets), for 20 days. During the last 5 to 10 days of therapy, an oral progestogen should be given. Withdrawal bleeding may be expected in the next 2 to 5 days. It is important that therapy be continued and dosage not be reduced, otherwise breakthrough bleeding will occur. The above oral estrogen-progestogen regimen should be repeated, beginning on day 5 of the cycle, for up to three additional cycles after which medication should be withdrawn and the patient's requirement for therapy reassessed. Should breakthrough bleeding occur before the end of a 20-day regimen, therapy should be stopped and then resumed on the fifth day of flow.

The usual precautionary measures governing intravenous administration should be adhered to. Injection should be made **SLOWLY** to obviate the occurrence of flushes.

Infusion of Premarin® Intravenous 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 and dextrose 10% infusions in a ratio of 1:1. **IT IS NOT COMPATIBLE WITH PROTEIN HYDROLYSATE, ASCORBIC ACID, OR ANY OTHER INFUSION SOLUTIONS WITH AN ACID pH.**

DIRECTIONS FOR STORAGE AND RECONSTITUTION

Storage before reconstitution

Store in refrigerator, 2°-8° C.

To reconstitute

Immediate use:

Reconstitute Premarin[®] Intravenous with 5 ml of Sterile Water for Injection U.S.P. to obtain approximately 5.0 ml of straw-coloured solution at 5 mg/ml. Diluent should be added slowly, letting it flow against the side of the vial. Agitate gently. **Do not shake violently. Use immediately after reconstitution**

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms of overdosage of estrogen-containing products in adults and children when the drug is taken orally 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.

PHARMACEUTICAL INFORMATION

Drug Substance:

Proper Name: Conjugated Estrogens CSD.

Composition: PREMARIN[®] (conjugated estrogens, CSD) is a mixture of estrogens obtained exclusively from natural sources occurring as the sodium salts of water-soluble estrogen sulfates blended to represent the average composition of material derived from pregnant mares' urine. It is a mixture of at least the following estrogens: estrone, equilin, 17 α -dihydroequilin, 17 α -estradiol, 17 β -dihydroequilin, δ 8,9-dehydroestrone, 17 β -estradiol, equilenin, 17 α -dihydroequilenin and 17 β -dihydroequilenin as salts of their sulfate esters.

Drug Product:

Medicinal Ingredients: Conjugated Estrogens, CSD

Non-Medicinal Ingredients: lactose, simethicone, and sodium citrate

AVAILABILITY OF DOSAGE FORMS

Each vial contains 25 mg of conjugated estrogens for injection CSD, in a sterile lyophilized cake. The pH is adjusted to 7.3 with sodium hydroxide or hydrochloric acid. The reconstituted solution is suitable for intravenous or intramuscular injection.