PRESCRIBING INFORMATION

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

25 mg CE/vial

ESTROGENIC HORMONES

® Wyeth Canada
Pfizer Canada Inc., Licensee
17,300 Trans-Canada Highway
Kirkland, Quebec H9J 2M5

Date of Revision:
December 6, 2011

Control #: 148679

TABLE OF CONTENTS

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 (Ml), 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

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. Estrogen receptors have been identified in various tissues including the wall of blood vessles, in tissues of the reproductive tract, breast, brain, liver and bone of women. 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.

Endogenous estrogens are largely responsible for the development and maintenance of the female reproductive system and secondary sex characteristics.

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, which is secreted by the adrenal cortex, to estrone by peripheral tissues. Thus, estrone and the sulfateconjugated 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.

Currently, there are no pharmacodynamic data known for CE alone.

Women's Health Initiative Study (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 oral conjugated estrogens (CE) [0.625 mg daily] alone or in combination with medroxyprogesterone acetate (MPA) [0.625 mg/2.5 mg daily] compared to placebo in the prevention of certain chronic diseases. The primary endpoint was the incidence of coronary heart disease [(CHD) defined as non-fatal myocardial infarction (MI), silent MI and CHD death], with invasive breast cancer as the primary adverse outcome. A "global index" included the earliest occurrence of CHD, invasive breast cancer, stroke, pulmonary embolism (PE), endometrial cancer (only in the CE plus MPA substudy), colorectal cancer, hip fracture, or death due to other causes. The substudy did not evaluate the effects of CE therapy alone or CE plus MPA on menopausal symptoms.

WHI Estrogen-Alone Substudy

The WHI 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] 0.78-1.16); a slightly elevated RR of CHD was reported in the early follow-up period and diminished over time. There was no significant effect on the RR of invasive breast cancer (RR 0.80, 95% nCI 0.62-1.04) or colorectal cancer (RR 1.08, 95% nCI 0.75-1.55) reported. Estrogen use was associated with a statistically significant increased risk of stroke (RR 1.33, 95% nCI 1.05-1.68) and deep vein thrombosis (DVT) (RR 1.47, 95% nCI 1.06-2.06). The RR of PE (RR 1.37, 95% nCI 0.90-2.07) was not significantly increased. A statistically significant reduced risk of hip, vertebral and total fractures was reported with estrogen use (RR 0.65, 95% nCI 0.45-0.94), (RR 0.64, 95% nCI 0.44-0.93), and (RR 0.71, 95% nCI 0.64-0.80), respectively. The estrogen-alone substudy did not report a statistically significant effect on death due to other causes (RR 1.08, 95% nCI 0.88-

1.32) or an effect on overall mortality risk (RR 1.04, 95% nCI 0.88-1.22). These confidence intervals are unadjusted for multiple looks and multiple comparisons.

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

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

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

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:

- Active or chronic 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 uterine bleeding.
- Active or history of confirmed venous thromboembolism (such as deep venous thrombosis, or pulmonary embolism) or active thrombophlebitis.
- Active or history of confirmed arterial thromboembolic disease (e.g. stroke, myocardial infarction, coronary heart disease).
- Partial or complete loss of vision due to ophthalmic vascular disease.
- Hypersensitivity to any component of the medication of the ingredients.
- Known thrombophilic disorders (e.g., protein C, protein S, OR antithrombin deficiency; prothrombin mutation or anticardiolipin antibodies).

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 and Precautions associated with CE treatment should be taken into account.

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).

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.

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

Stroke

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

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

Should a stroke occur or be suspected, Premarin Intravenous should be discontinued immediately (see **ACTIONS AND CLINICAL PHARMACOLOGY**)

Hematologic

Venous thromboembolism

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

Should a VTE occur or be suspected, Premarin Intravenous should be discontinued immediately (see **ACTIONS AND CLINICAL PHARMACOLOGY**).

If feasible, Premarin Intravenous 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.

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/m^2). The risk of VTE also increases with age and smoking (see **PRECAUTIONS**).

The risk of VTE may be temporarily increased with prolonged immobilization, major surgery or trauma. In women on HRT, attention should be given to prophylactic measures to prevent VTE following surgery. Also, patients with varicose veins should be closely supervised. The physisan should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, retinal thrombosis, cerebral embolism and pulmonary embolism). If these occur or are suspected, hormone therapy should be discontinued immediately, given the risks of long-term disability or fatality.

Carcinogenesis and Mutagenesis

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 **ACTIONS AND CLINICAL PHARMACOLOGY**), In the estrogen-alone substudy of WHI, after an average of 7.1 years of follow-up, CEE (0.625 mg daily) was not associated with an increased risk of invasive breast cancer.

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

There is a need for caution in prescribing estrogens for women with known risk factors associated with the development of breast cancer, such as strong family history of breast cancer (first degree relative) or who present a breast condition with an increased risk (abnormal mammograms and/ or atypical hyperplasia at breast biopsy).

Other known risk factors for the development of breast cancer such as nulliparity, obesity, early menarche, late age at first full term pregnancy and at menopause should also be evaluated.

It is recommended that women undergo mammography prior to the start of HRT treatment and at regular intervals during treatment, as deemed appropriate by the treating physician and according to the perceived risks for each patient.

The overall benefits and possible risks of hormone replacement therapy should be fully considered and discussed with patients. It is important that the modest increased risk of being diagnosed with breast cancer after 4 years of treatment with combined estrogen plus progestin HRT (as reported in the results of the WHI trial) be discussed with the patient and weighed against its known benefits.

Instructions for regular self-examination of the breasts should be included in this Counseling.

Endometrial cancer
The use of unopposed estrogens in women with an intact uterus has been associated with an increased risk of endometrial cancer (see **ACTIONS AND CLINICAL PHARMACOLOGY**).

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.

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.

Ovarian cancer
In some epidemiologic studies, the use of estrogen therapy has been associated with an increased risk of ovarian cancer over multiple years of use. Other epidemiologic studies have not found these associations.

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

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

It is unknown whether these findings apply to younger postmenopausal women.

Hepatic/Biliary/Pancreatic
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.

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

PRECAUTIONS

General precautions
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
In the Health and Osteoporosis, Progestin and Estrogen (HOPE) Study, the mean percent increases from baseline in serum triglycerides after one year of treatment with CE 0.625 mg, 0.45 mg, and 0.3 mg compared with placebo were 34.3, 30.2, 25.1, and 10.8 percent increase from baseline, 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 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**.

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

Hypothyroidism
Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Patients dependent on thyroid hormone therapy, who are also receiving estrogens, may require increased doses of their thyroid replacement therapy. These women should have their thyroid function monitored in order to maintain their free thyroid hormone levels in an acceptable range (see **Laboratory test interactions**).

Endocrine and Metabolism

Glucose and lipid metabolism

Women with familial hyperlipidemias need special surveillance. Lipid-lowering measures are recommended additionally, before treatment is started.

Pregnancy

Premarin Intravenous should not be used during pregnancy (see **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

Safety and Effectiveness in pediatric patients have not been established. Premarin Intravenous is not indicated in children.

Geriatric Use (> 65 years of age)

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

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 ß-estradiol, one of the components of conjugated estrogens, is metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, strong inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4 such as St. John's Wort (*Hyperticum perforatum*) preparations, phenobarbital, phenytoin, carbamazepine, rifampicin and dexamethasone may reduce plasma concentrations of estrogens, possibly resulting in a decrease in the therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4 such as cimetadine, erythromycin, ketoconazole, clarithromycin,

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

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_1) 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 may be decreased. 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

The benefits and risks of HRT must always be carefully weighed, including consideration of the emergence of risks as therapy continues (see **Warnings**). Estrogens with or without progestins should be prescribed at the lowest effect doses and for the shortest duration consistent with treatment goals and risks for the individual woman. In the absence of comparable data, the risks of HRT should be assumed to be similar for all estrogens and estrogen/progestin combinations.

Dosage adjustment may be made based on individual patient response.

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 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.