PRESCRIBING INFORMATION

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

25 mg CE/vial, Intravenous / Intramuscular

ESTROGENIC HORMONES

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

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TABLE OF CONTENTS

NAME OF DRUG

PREMARIN® Intravenous

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

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. Premarin Intravenous should be prescribed with an appropriate dosage of a progestin for women with intact uteri, in order to prevent endometrial hyperplasia/carcinoma.

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 malignant neoplasia (e.g., endometrial cancer)
- Endometrial hyperplasia
- Known or suspected pregnancy (see Warnings: Effects during pregnancy).
- Undiagnosed abnormal genital 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 this drug or to any ingredient in the formulation or component of the container. For a complete listing, see **PHARMACEUTICAL INFORMATION** and **AVAILABILITY OF DOSAGE FORMS**.
- Known thrombophilic disorders (e.g., protein C, protein S, OR antithrombin deficiency; prothrombin mutation or anticardiolipin antibodies).

WARNINGS

Serious Warnings and Precautions

The Women's Health Initiative (WHI) trial examined the health benefits and risks of oral combined *estrogen plus progestin* therapy (n=16,608) and oral *estrogen-alone* therapy (n=10,739) in postmenopausal women aged 50 to 79 years.

The *estrogen plus progestin* arm of the WHI trial (mean age 63.3 years) indicated an increased risk of *myocardial infarction* (MI), *stroke, invasive breast cancer, pulmonary emboli* and *deep vein thrombosis* in postmenopausal women receiving treatment with combined conjugated equine estrogens (CEE, 0.625 mg/day) and medroxyprogesterone acetate (MPA, 2.5 mg/day) for 5.2 years compared to those receiving placebo.

The *estrogen-alone* arm of the WHI trial (mean age 63.6 years) indicated an increased risk of *stroke* and *deep vein thrombosis* in hysterectomized women treated with CEE-alone (0.625 mg/day) for 6.8 years compared to those receiving placebo.

Therefore, the following should be given serious consideration at the time of prescribing:

- 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 approved indication.

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.

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.

It is recommended that estrogens not be given to women with existing breast cancer or those with a previous history of the disease (see **CONTRAINDICATIONS**).

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
Some recent epidemiologic studies have found that the use of hormone replacement therapy (*estrogen-alone* and *estrogen plus progestin* therapies), in particular for five or more years, has been associated with an increased risk of 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.

The results of the Heart and Estrogen/progestin Replacement Studies (HERS and HERS II) and the Women's Health Initiative (WHI) trial indicate that the use of estrogen plus progestin is associated with an increased risk of coronary heart disease (CHD) in postmenopausal women. The results of the WHI trial indicate that the use of estrogen-alone and estrogen plus progestin is associated with an increased risk of stroke in postmenopausal women.

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

WHI trial findings

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**)

HERS and HERS II findings

In the Heart and Estrogen/progestin Replacement Study (HERS) of postmenopausal women with documented heart disease (n=2763, average age 66.7 years), a randomized placebo-controlled clinical trial of secondary prevention of coronary heart disease (CHD), treatment with 0.625 mg/day oral conjugated equine estrogen (CEE) plus 2.5 mg oral medroxyprogesterone acetate (MPA) demonstrated no cardiovascular benefit. Specifically, during an average follow up of 4.1 years, treatment with CEE plus 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 hormone-treated group than in the placebo group in year 1, but not during the subsequent years.

From the original HERS trail, 2321 women consented to participate in an open label extension of HERS known as HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. After 6.8 years, hormone therapy did not reduce the risk of cardiovascular events in women with CHD.

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 physician 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.

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
Available epidemiological data indicate that the use of combined *estrogen plus progestin* in women age 65 and over may increase the risk of developing probable dementia.

The Women's Health Initiative Memory Study (WHIMS), a clinical substudy of the WHI, was designed to assess whether postmenopausal hormone replacement therapy (oral *estrogen plus progestin* or oral *estrogen-alone*) reduces the risk of dementia in women aged 65 and over (age range 65-79 years) and free of dementia at baseline.

In the *estrogen plus progestin* arm of the WHIMS (n=4532), women with intact uteri were treated with daily 0.625 mg conjugated equine estrogens (CEE) plus 2.5 mg medroxyprogesterone acetate (MPA) or placebo for an average of 4.05 years. The results, when extrapolated to 10,000 women treated over a one-year period showed:

- 23 more cases of probable dementia (45 on combined HRT versus 22 on placebo).

In the *estrogen-alone* arm of the WHIMS (n=2947), women with prior hysterectomy were treated with daily 0.625 mg CEE or placebo for an average of 5.21 years. The results, when extrapolated to 10,000 women treated over a one-year period showed:

- 12 more cases of probable dementia (37 on *estrogen-alone* versus 25 on placebo), although this difference did not reach statistical significance.

When data from the *estrogen plus progestin* arm of the WHIMS and estrogen-alone arm of the WHIMS were combined, as per the original WHIMS protocol, in 10,000 women over a one-year period, there were:

- 18 more cases of probable dementia (41 on estrogen plus progestin or estrogen-alone versus 23 on placebo).

Epilepsy
Particular caution indicated in women with epilepsy, as estrogens with or without progestins may cause an exacerbation of this condition

Ear/Nose/Throat

Otosclerosis
Estrogens should be used with caution in patients with otosclerosis

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.

Hepatic hemangiomas
Particular caution is indicated in women with hepatic hemangiomas, as HRT may cause an exacerbation

Immune

Systemic lupus erythematosus
Particular caution is indicated in women with systemic lupus erythematosus, as HRT may cause an exacerbation of this condition.

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, renal dysfunction or asthma, warrant careful observation when estrogens are prescribed.

Exacerbation of other 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
A worsening of glucose tolerance and lipid metabolism have been observed in a significant percentage of peri- and post-menopausal patients. Therefore, diabetic patients or those with a predisposition to diabetes should be observed closely to detect any alterations in carbohydrate or lipid metabolism, especially in triglyceride blood levels.

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

Calcium and phosphorus metabolism
Because the prolonged use of estrogens influences the metabolism of calcium and phosphorus, estrogens should be used with caution in patients with metabolic and malignant bone diseases associated with hypercalcemia and in patients with renal insufficiency.

Hypothyroidism
Patients who require thyroid hormone replacement therapy and who are also taking estrogen should have their thyroid function monitored regularly to assure that thyroid hormone levels remain in an acceptable range (see **Drug-Laboratory Test Interactions**).

Genitourinary
Vaginal bleeding
Abnormal vaginal bleeding, due to its prolongation, irregularity or heaviness, occurring during therapy should prompt appropriate diagnostic measures to rule out the possibility of uterine malignancy and the treatment should be re-evaluated.

Uterine leiomyomata
Pre-existing uterine leiomyomata may increase in size during estrogen use. Growth, pain or tenderness of uterine leiomyomata requires discontinuation of medication and appropriate investigation.

Endometriosis
Symptoms and physical findings associated with a previous diagnosis of endometriosis may reappear or become aggravated with estrogen use.

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.

Lamotrigine:
Hormonal contraceptives containing estrogens have been shown to significantly decrease plasma concentrations of lamotrigine when co-administered due to induction of lamotrigine glucuronidation. This may reduce seizure control. The same interaction has been reported in women taking lamotrigine along with HRT containing estrogens.

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
Before Premarin Intravenous is administered, the patient should have a complete physical examination including a blood pressure determination. Breasts and pelvic organs should be appropriately examined and a Papanicolaou smear should be performed. Endometrial biopsy should be done only when indicated. Baseline tests should include mammography, measurements of blood glucose, calcium, triglycerides and cholesterol, and liver function tests.

The first follow-up examination should be done within 3-6 months after initiation of treatment to assess response to treatment. Thereafter, examinations should be made at intervals at least once a year. Appropriate investigations should be arranged at regular intervals as determined by the physician.

The importance of regular self-examination of the breasts should be discussed with the patient.

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.

See **Warnings and Precautions** regarding potential induction of malignant neoplasms and adverse effects similar to those of oral contraceptives.

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.

Premarin Intravenous should be prescribed with an appropriate dosage of a progestin for women with intact uteri in order to prevent endometrial hyperplasia/carcinoma. Progestin therapy is not required as part of hormone replacement therapy in women who have had a previous hysterectomy.

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.

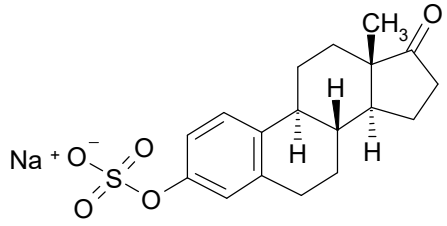
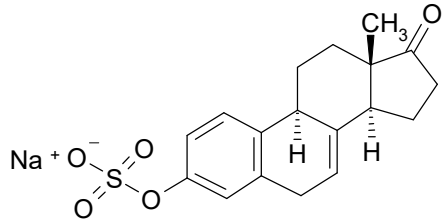
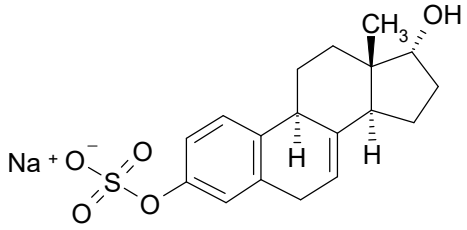
PHARMACEUTICAL INFORMATION

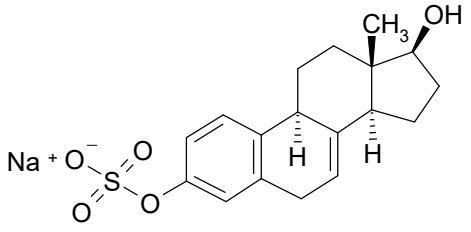
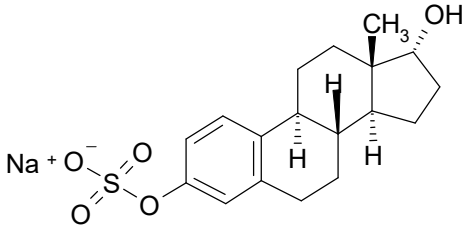
Drug Substance:

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 □-dihydroequilin, 17 □-estradiol, 17 □-dihydroequilin, □ 8,9-dehydroestrone, 17 □-estradiol, equilenin, 17 □-dihydroequilenin and 17 □-dihydroequilenin as salts of their sulfate esters.

Structural Formula:

Component	Structural Formula
Primary components:	
Sodium estrone sulphate	
Sodium equilin sulphate	
Concomitant components:	
Sodium 17α-dihydroequilin sulphate	

Component	Structural Formula
Sodium 17β-dihydroequilin sulphate	
Sodium 17α-estradiol sulphate	

Molecular formula:

Component	Molecular Formula
Primary components:	
Sodium estrone sulphate	$C_{18}H_{21}NaO_5S$
Sodium equilin sulphate	$C_{18}H_{19}NaO_5S$
Concomitant components:	
Sodium 17α-dihydroequilin sulphate	$C_{18}H_{21}NaO_5S$
Sodium 17β-dihydroequilin sulphate	$C_{18}H_{21}NaO_5S$
Sodium 17α-estradiol sulphate	$C_{18}H_{23}NaO_5S$

Molecular mass:

Component	Molecular Formula
Primary components:	
Sodium estrone sulphate	372.4
Sodium equilin sulphate	370.4
Concomitant components:	
Sodium 17α-dihydroequilin sulphate	372.4
Sodium 17β-dihydroequilin sulphate	372.4
Sodium 17α-estradiol sulphate	374.4

DOSAGE FORMS, COMPOSITION AND PACKAGING

Medicinal Ingredients: conjugated Estrogens, CSD
Non-Medicinal Ingredients: lactose, simethicone, and sodium citrate

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.

REFERENCES

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6. Shumaker SA, Legault C, Rapp SR, Thal L, Wallace RB, Ockene JK, et al. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women. The Women's Health Initiative Memory Study: A randomized controlled trial. JAMA. 2003; 289(20):2651-2662.

7. Shumaker SA, Legault C, Kuller L, Rapp SR, Thal L, Lane DS, et al. Conjugated Equine Estrogens and Incidence of Probable Dementia and Mild Cognitive Impairment in Postmenopausal Women. Women's Health Initiative Memory Study. JAMA. 2004; 291(24):2947-2958.

PART III: CONSUMER INFORMATION

Premarin® Intravenous
Intravenous / Intramuscular
(Conjugated Estrogens for Injection, C.S.D.)

This leaflet is part III of a three-part "Product Monograph" published when Premarin Intravenous was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Premarin Intravenous injected into a vein or a muscle. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
Premarin Intravenous is used for the treatment of abnormal bleeding caused by hormonal imbalance when your doctor has found no serious cause of the bleeding.

Premarin Intravenous should not be used by women with intact uteri unless it is prescribed in association with a progestin.

Premarin Intravenous should be used only under the supervision of a doctor, with regular follow-up at least once a year to identify side effects associated with its use. Your first follow-up visit should be within 3 to 6 months of starting treatment. Your visit may include a blood pressure check, a breast exam, a Pap smear and pelvic exam. You should have a mammogram before starting treatment and at regular intervals as recommended by your doctor. Your doctor may recommend some blood tests.

You should carefully discuss the risks and benefits of hormone replacement therapy (HRT) with your doctor. You should regularly talk with your doctor about whether you still need treatment with HRT.

What it does:

When using Premarin Intravenous women are using a hormone, estrogen (i.e. conjugated estrogens for injection, C.S.D.). Premarin Intravenous replaces estrogens in your body, which naturally decrease at menopause.

Estrogens are female hormones that are produced by a woman's ovaries and are necessary for normal sexual development and the regulation of menstrual periods during the childbearing years.

When a woman is between the ages of 45 and 55, the ovaries normally stop making estrogens. This leads to a drop in body estrogen levels and marks the beginning of menopause (the end of monthly menstrual periods). A sudden drop in estrogen levels also occurs if both ovaries are removed during an operation before natural menopause takes place. This is referred to as surgical menopause.

When the estrogen levels begin dropping, some women develop very uncomfortable symptoms, such as feelings of warmth in the face, neck, and chest, or sudden intense episodes of heat and sweating ("hot flashes") as well as vaginal symptoms and abnormal bleeding. In some women the symptoms are mild; in others they can be severe. These symptoms may last a few months or longer. Premarin Intravenous can help treat abnormal bleeding caused by dropping levels of estrogens.

When it should not be used:
Before using Premarin Intravenous be sure to tell your doctor if you have any of the following medical problems, as Premarin Intravenous should not be used under these conditions:

- Have a liver condition that has not returned to normal.
- Have a known, suspected or past history of breast cancer.
- Have a known or suspected hormone dependent cancer (e.g.endometrial cancer).
- Have unusual thickening of the lining of the womb (endometrial hyperplasia).
- You are or may be pregnant.
- You have unusual vaginal bleeding.
- Have or have had blood clot disorders, including blood clots in the legs or lungs, or inflammation of the veins (thrombophlebitis).
- Have active or past history of heart disease, heart attacks or stroke.
- Have partially or completely lost vision due to blood vessel disease of the eye.
- Have known abnormality of the blood clotting system that increases your risk for having a blood clot (e.g. protein C, protein S, or antithrombin deficiency).
- Are allergic (hypersensitive) to conjugated estrogens or any of the other ingredients in Premarin Intravenous (including lactose).
- Have been diagnosed with a bleeding disorder.

What the medicinal ingredients are:
Conjugated Estrogens, CSD

What the nonmedicinal ingredients are:
Lactose, simethicone, and sodium citrate.

What dosage forms it comes in:
Premarin Intravenous is available in vials containing 25mg of powder.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

The Women's Health Initiative (WHI) is a large clinical study that assessed the benefits and risks of oral combined *estrogen plus progestin* therapy and oral *estrogen-alone* therapy compared with placebo (a pill with no active ingredients) in postmenopausal women.

The WHI trial indicated an increased risk of myocardial infarction (heart attack), stroke, breast cancer, pulmonary emboli (blood clots in the lungs) and deep vein thrombosis (blood clots in the large veins) in postmenopausal women taking oral combined *estrogen plus progestin*.

The WHI trial indicated an increased risk of stroke and deep vein thrombosis in postmenopausal women with prior hysterectomy (surgical removal of the uterus) taking oral *estrogen-alone*.

Therefore, you should highly consider the following:

- There is an increased risk of developing invasive breast cancer, heart attack, stroke and blood clots in both lungs and large veins with the use of estrogen plus progestin therapy.
- There is an increased risk of stroke and blood clots in the large veins with the use of estrogen-alone therapy.
- Estrogens with or without progestins should not be used for the prevention of heart disease or stroke.
- Estrogens with or without progestins should be used at the **lowest effective dose** and for the **shortest period of time** possible. Regular medical follow-up is advised.

Breast Cancer

The results of the WHI trial indicated an increased risk of breast cancer in postmenopausal women taking combined *estrogen plus progestin* compared to women taking placebo.

The results of the WHI trial indicated no difference in the risk of breast cancer in post-menopausal women with prior hysterectomy taking *estrogen-alone* compared to women taking placebo.

Estrogens should not be taken by women who have a personal history of breast cancer.

In addition, women with a family history of breast cancer or women with a history of breast lumps, breast biopsies or abnormal mammograms (breast x-rays) should consult with their doctor before starting HRT.

Women should have a mammogram before starting HRT and at regular intervals during treatment as recommended by their doctor.

Regular breast examinations by a doctor and regular breast self-examination are recommended for all women. You should review technique for breast self-examination with your doctor.

Overgrowth of the lining of the uterus and cancer of the uterus

The use of *estrogen-alone* therapy by post-menopausal women who still have a uterus increases the risk of developing endometrial hyperplasia (overgrowth of the lining of the uterus), which increases the risk of endometrial cancer (cancer of the lining of the uterus).

If you still have your uterus, you should take a progestin medication (another hormone drug) regularly for a certain number of days of each month to reduce the risk of endometrial hyperplasia.

You should discuss progestin therapy and risk factors for endometrial hyperplasia and endometrial carcinoma with your doctor. You should also report any unexpected or unusual vaginal bleeding to your doctor.
If you have had your uterus removed, you are not at risk of developing endometrial hyperplasia or endometrial carcinoma. Progestin therapy is therefore not generally required in women who have had a hysterectomy.

Ovarian Cancer

In some studies, the use of estrogen-alone and estrogen plus progestin therapies for 5 or more years has been associated with an increased risk of ovarian cancer.

Heart Disease and Stroke
The results of the WHI trial indicated an increased risk of stroke and coronary heart disease in post-menopausal women taking combined *estrogen plus progestin* compared to women taking placebo.

The results of the WHI trial indicated an increased risk of stroke, but no difference in the risk of coronary heart disease in post-menopausal women with prior hysterectomy taking *estrogen-alone* compared to women taking placebo.

Abnormal Blood Clotting
The results of the WHI trial indicated an increased risk of blood clots in the lungs and large veins in post-menopausal women taking combined *estrogen plus progestin* compared to women taking placebo.

The results of the WHI trial indicated an increased risk of blood clots in the large veins, but no difference in the risk of blood clots in the lungs in post-menopausal women with prior hysterectomy taking *estrogen-alone* compared to women taking placebo.

The risk of blood clots also increases with age, if you or a family member has had blood clots, if you smoke or if you are severely overweight. The risk of blood clots is also temporarily increased if you are immobilized for long periods of time and following major surgery. You should discuss risk factors for blood clots with your doctor since blood clots can be life-threatening or cause serious disability.

Gallbladder Disease
The use of estrogens by postmenopausal women has been associated with an increased risk of gallbladder disease requiring surgery.

Dementia
The Women's Health Initiative Memory Study (WHIMS) was a substudy of the WHI trial and indicated an increased risk of dementia (loss of memory and intellectual function) in post-menopausal women age 65 and over taking oral combined *estrogen plus progestin* compared to women taking placebo.

The WHIMS indicated no difference in the risk of dementia in post-menopausal women age 65 and over with prior hysterectomy taking oral *estrogen-alone* compared to women taking placebo.

BEFORE you use Premarin Intravenous talk to your doctor or pharmacist if you:

- have a history of allergy or intolerance to any medications or other substances
- have a personal history of breast disease (including breast lumps) and/or breast biopsies, or a family history of breast cancer
- have experienced any unusual or undiagnosed vaginal bleeding
- have a history of uterine fibroids or endometriosis
- have a history of liver disease or liver tumors, jaundice (yellowing of the eyes and/or skin) or itching related to estrogen use or during pregnancy
- have a history of migraine headache
- have a history of high blood pressure
- have a personal or family history of blood clots, or a personal history of heart disease or stroke
- have a history of kidney disease, asthma or epilepsy (seizures)
- have a history of bone disease (this includes certain metabolic conditions or cancers that can affect blood levels of calcium and phosphorus)
- have been diagnosed with diabetes
- have been diagnosed with porphyria (a disease of blood pigment)
- have been diagnosed with otosclerosis (hearing loss due to a problem with the bones in your ear)
- have a history of high cholesterol or high triglycerides
- are pregnant or may be pregnant. If pregnancy occurs while taking Premarin Intravenous contact your doctor immediately
- have had a hysterectomy (surgical removal of the uterus)
- smoke
- have been told that you have a condition called hereditary angioedema or if you have had episodes of rapid swelling of the hands, feet, face, lips, eyes, tongue, throat (airway blockage), or digestive tract
- have been diagnosed with lupus
- other existing conditions include very low calcium levels, thyroid problems, fluid retention and breastfeeding

INTERACTIONS WITH THIS MEDICATION

Tell your doctor or pharmacist if you are taking any other medications, including prescription medications, over-the-counter medications, vitamins or herbal products. The following may interact with Premarin Intravenous:
- Blood thinners (drugs that prevent or reduce blood clots)
- Medicine to control your diabetes
- Medicine to control high blood pressure
- Barbiturates (class of sedatives)
- Hydantoins (anticonvulsants)
- Carbamazepine (anticonvulsant)
- Lamotrigine (anticonvulsant)
- Meprobamate (drug that treats tension, anxiety, and nervousness)
- Phenylbutazone (nonsteroidal anti-inflammatory drug)
- Rifampicin (antibiotic)
- St. John’s Wort (Hyperticum perforatum)
- Phenobarbital (drug used to control seizures)
- Phenytoin (drug that can treat and prevent seizures)

- Dexamethasone (drug that can treat inflammation)
- Cimetadine (drug that can reduce acid in the stomach to treat ulcers and acid reflux)
- Erythromycin (antibiotic)
- Ketoconazole (drug that can treat fungal infection)
- Clarithromycin (antibiotic)
- Itraconazole (drug that can treat fungal infection)
- Ritonavir (drug used to treat HIV/AIDS)
- Grapefruit juice

Premarin Intravenous may interfere with laboratory testing.

PROPER USE OF THIS MEDICATION

Usual Adult Dose:
Your healthcare professional will inject Premarin Intravenous into a vein or a muscle.

You will receive one 25 mg dose. The dose may be repeated in 6 to 12 hours, if deemed necessary by your healthcare professional. Following this, your healthcare professional should begin treating you with lower doses of the medicine that you can take in pill form.

Overdose:

If you think you have been given too much Premarin Intravenous contact healthcare professional, hospital emergency department or regional poison control center immediately, even if there are no symptoms.

Overdosage with estrogens may cause nausea and vomiting, breast discomfort, dizziness, abdominal pain, drowsiness/fatigue or vaginal bleeding may occur in women.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects may include:

- Breast pain
- Vaginal bleeding or spotting
- Bloating, nausea, vomiting, abdominal pain
- Weight gain
- Dizziness
- Headache (including migraine)
- Nervousness
- Rash

These are not all the possible side effects you may feel when taking Premarin Intravenous. If you experience any side effects not listed here, contact your healthcare professional.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Frequency	Symptom / possible side effect	Talk with your doctor or pharmacist		Stop taking drug and seek immediate medical help
		Only if severe	In all cases	
Rare	**Inflammation of the Large Intestine (ischemic colitis):** abdominal pain, tenderness and/or cramping, blood in your stool, diarrhea, feeling of urgency to move your bowls, nausea			√
	Benign (non-cancerous) Brain Tumour: headache, seizures, blurred vision, weakness in arms or legs, numbness, trouble speaking			√
	Blood Clot in the Leg: pain, swelling, redness and tenderness in the leg			√
	Blood Clot in the Lung: sharp pain in the chest, coughing blood, sudden shortness of breath.			√
	Injection Site Reaction: pain, swelling, redness, tenderness		√	
	Edema: swelling of the hands, ankles and/or feet	√		
Very Rare	**Superficial Thrombophlebitis (blood clot in a vein just under the skin):** redness and inflammation along a vein, skin warm to the touch, pain, hardening of the vein			√

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Frequency	**Symptom / possible side effect**	**Talk with your doctor or pharmacist**		**Stop taking drug and seek immediate medical help**
		Only if severe	**In all cases**	
	Angioedema and Severe Allergic Reactions: swelling of the face, eyes, or tongue, difficulty swallowing, wheezing, hives and generalized itching, rash, fever, abdominal cramps, chest discomfort or tightness, difficulty breathing, unconsciousness			√
	Low Blood Pressure: dizziness, fainting, lightheadedness May occur when you go from lying or sitting to standing up		√	
Unknown	**Breast Cancer:** breast lump, unusual discharge		√	
	Heart attack: crushing chest pain or chest heaviness, pain in the arm, back, neck or jaw, shortness of breath, cold sweat, nausea, light-headedness			√
	Persistent sad mood			√
	Blood clot in the eye: sudden partial or complete loss of vision			√

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Frequency	**Symptom / possible side effect**	**Talk with your doctor or pharmacist**		**Stop taking drug and seek immediate medical help**
		Only if severe	**In all cases**	
	Stroke: sudden severe headache or worsening of headache, vomiting, dizziness, fainting, disturbance of vision or speech or weakness or numbness in an arm or leg			√
	Unexpected vaginal bleeding		√	
	Liver Disorder: yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite		√	
	Cerebrovascular Insufficiency: visual disturbances, migraines, trouble speaking, paralysis or loss of consciousness			√
	Gallbladder disorder: severe pain in the upper right abdomen, pain in the back between the shoulder blades, nausea and vomiting		√	

This is not a complete list of side effects. For any unexpected effects while taking Premarin Intravenous, contact your doctor or pharmacist.

HOW TO STORE IT

Premarin Intravenous will be stored by your health care professional in the refrigerator between 2-8ºC.

Keep out of reach and sight of children.

Reporting Side Effects
You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: http//www.pfizer.ca or by contacting the sponsor, Pfizer Canada ULC, at: 1-800-463-6001

This leaflet was prepared by Pfizer Canada ULC.

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