

PRODUCT MONOGRAPH

Pr **Premplus**[®]

conjugated estrogens tablets CSD 0.625 mg and
medroxyprogesterone acetate tablets USP 2.5 mg, 5.0 mg
(Continuous therapy)

Pr **Premplus Cycle**[®]

conjugated estrogens tablets CSD 0.625 mg and
medroxyprogesterone acetate tablets USP 10.0 mg
(Cyclic therapy)

Estrogenic Hormones/Progestin

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Premplus®

Continuous therapy of conjugated estrogens tablets CSD and
medroxyprogesterone acetate tablets USP

Premplus Cycle®

Cyclic therapy of conjugated estrogens tablets CSD and
medroxyprogesterone acetate tablets USP

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Premplus® oral	conjugated estrogens tablets 0.625 mg and medroxyprogesterone acetate tablets 2.5 mg, 5.0 mg	lactose <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>
Premplus Cycle® oral	conjugated estrogens tablets 0.625 mg and medroxyprogesterone acetate tablets USP 10.0 mg	lactose <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

INDICATIONS AND CLINICAL USE

Premplus® and Premplus Cycle® therapy is indicated in women with intact uteri for the following:

- relief of moderate to severe vasomotor symptoms associated with menopause,⁹ occurring in naturally or surgically induced estrogen deficiency states;
- prevention of osteoporosis in naturally occurring or surgically induced estrogen-deficiency states. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy with Premplus® and Premplus Cycle® should be considered in light of other available therapies (please see the Serious Warnings and Precautions box), and should only be considered in women at significant risk of osteoporosis and for whom non-estrogen medications are not considered to be appropriate. Adequate diet, calcium and vitamin D intake, cessation of smoking, as well as regular physical weight-bearing exercise are required in addition to the administration of Premplus® and Premplus Cycle®.

- treatment of vulvar and vaginal atrophy associated with menopause. **When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.**

Premplus[®] and Premplus Cycle[®] therapy is recommended for the above indications only in women with intact uteri since the regimen includes a progestin whose role is to prevent endometrial hyperplasia.

Geriatrics (> 65 years of age): See above indications.

Pediatrics: Clinical studies have not been conducted in the pediatric population. Premplus[®] and Premplus Cycle[®] are not indicated for use in children.

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.
- Liver dysfunction or disease as long as liver function tests have failed to return to normal.
- Known or suspected estrogen-dependent or progestin-dependent malignant neoplasia (e.g. endometrial cancer).
- Endometrial hyperplasia
- Known, suspected, or past history of breast cancer.
- Undiagnosed abnormal genital bleeding.
- Known or suspected pregnancy.
- Active or past history of confirmed venous thromboembolism (such as deep venous thrombosis or pulmonary embolism) or active thrombophlebitis.
- Active or past history of arterial thromboembolic disease (e.g. stroke, myocardial infarction, coronary heart disease).
- Partial or complete loss of vision due to ophthalmic vascular disease.
- Known thrombophilic disorders (e.g., protein C, protein S, antithrombin deficiency, or anti-cardiolipin antibodies).
- Migraine with aura

WARNINGS AND PRECAUTIONS

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.^{19,24,32}

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.¹⁹

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.³²

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.
- The use of Premplus® or Premplus Cycle® for the prevention of osteoporosis should be considered in light of other available therapies.

General

Combined Estrogen and Progestin Therapy

The benefits and risks of HRT must always be carefully weighed, including consideration of the emergence of risks as therapy continues.

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

Available epidemiological data indicate that the use of combined *estrogen plus progestin* by postmenopausal women is associated with an increased risk of invasive breast cancer.

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

In the *estrogen plus progestin* arm of the WHI trial, among 10,000 women over a one-year period, there were:

- 8 more cases of invasive breast cancer (38 on combined HRT versus 30 on placebo).¹⁹

The WHI study also reported that the invasive breast cancers diagnosed in the *estrogen plus progestin* group were similar in histology but were larger (mean [SD], 1.7 cm [1.1] vs 1.5 cm [0.9], respectively; P=0.04) and were at a more advanced stage compared with those diagnosed in the placebo group. The percentage of women with abnormal mammograms (recommendations for short-interval follow-up, a suspicious abnormality, or highly suggestive of malignancy) was significantly higher in the *estrogen plus progestin* group versus the placebo group. This difference appeared at year one and persisted in each year thereafter.²⁴

In the *estrogen-alone* arm of the WHI trial, there was no statistically significant difference in the rate of invasive breast cancer in hysterectomized women treated with conjugated equine estrogens versus women treated with placebo.³²

It is recommended that estrogens with or without progestins 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 with or without progestins 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 counselling.

Endometrial hyperplasia & endometrial carcinoma

The role of progestin, when combined with estrogen, is to help prevent endometrial hyperplasia/carcinoma in women with intact uteri.

The reported endometrial cancer risk among unopposed estrogen users is about 2- to 12-fold or greater than in non-users and appears to be dependent on duration of treatment and on estrogen

dose. Most studies show no significant increased risk associated with the use of estrogens for less than one year. The greatest risk appears associated with prolonged use, with increased risks of 15- to 24-fold for five years or more, and this risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued.

In a subset of WHI no increased risk of endometrial cancer after an average of 5.6 years of treatment with combined estrogen plus progestin HRT compared to placebo was observed.

Endometrial hyperplasia (a possible precursor of endometrial cancer) has been reported to occur at a rate of approximately 1% or less with CEE or CEE/MPA in two large clinical trials [Health and Osteoporosis, Progestin and Estrogen (n=2,153) and Menopausal Study Group (n=1,385)].^{35,36} In these two clinical trials two cases of endometrial cancer were reported to occur among women taking combination CEE/MPA.

Clinical surveillance of all women taking combined estrogen plus progestin HRT is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding.

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.

The estrogen plus progestin substudy of WHI (CE/MPA versus placebo) reported a non-statistically significant increased risk of ovarian cancer. However, limitations of this study include only 5.6 years of follow-up, and the low number of ovarian cancer cases (20 of 8506 subjects in the estrogen plus progestin group and 12 of 8102 subjects in the placebo group were diagnosed with invasive ovarian cancer).

Cardiovascular

Cardiovascular risk

HRT has been associated with an increased risk of cardiovascular events such as myocardial infarction and stroke, as well as venous thrombosis and pulmonary embolism (venous thromboembolism or VTE). Should any of these occur or be suspected, HRT should be discontinued immediately.

Estrogen Replacement Therapy (ERT) has been reported to increase the risk of stroke and deep venous thrombosis (DVT).

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

General

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.^{18, 19, 34} 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.^{19, 32}

WHI trial findings

In the combined *estrogen plus progestin* arm of the WHI trial, among 10,000 women over a one-year period, there were:

- 8 more cases of stroke (29 on combined HRT versus 21 on placebo)
- 7 more cases of CHD (37 on combined HRT versus 30 on placebo).¹⁹

In the *estrogen-alone* arm of the WHI trial of women with prior hysterectomy, among 10,000 women over a one-year period, there were/was:

- 12 more cases of stroke (44 on *estrogen-alone* therapy versus 32 on placebo)
- no statistically significant difference in the rate of CHD.³²

In the WHI estrogen-alone substudy, 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 in the same age group 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).

Subgroup analyses of women 50 to 59 years of age suggest a statistically non-significant reduction in CHD events (CE 0.625 mg compared to placebo) in women with less than 10 years since menopause (8 versus 16 per 10,000 women-years).

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.¹⁸

From the original HERS trial, 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.³⁴

Blood pressure

Women using hormone replacement therapy sometimes experience increased blood pressure. Blood pressure should be monitored with HRT use. Elevation of blood pressure in previously normotensive or hypertensive patients should be investigated and HRT may have to be discontinued.

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.

Women with porphyria need special surveillance.

Caution should be exercised in patients with pre-existing hypertriglyceridemia since rare cases of large increases of plasma triglycerides leading to pancreatitis have been reported with estrogen therapy in this population. Estrogen-containing products have been shown to increase plasma HDL and HDL-2 subfraction concentrations, reduce LDL cholesterol concentration, and increase triglyceride levels.

Calcium and phosphorus metabolism

Because the prolonged use of estrogens with or without progestins influences the metabolism of calcium and phosphorus, estrogens with or without progestins should be used with caution in patients with metabolic and malignant bone diseases associated with hypercalcemia and in patients with renal insufficiency. Estrogen therapy should be used with caution in women with hypoparathyroidism, as estrogen-induced hypocalcemia may occur.

Hypothyroidism

Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Women dependent on thyroid hormone replacement 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 **Drug-Laboratory Test Interactions**).

Other Conditions

Premplus and Premplus Cycle contain lactose. In patients with rare hereditary galactose intolerance, lactase deficiency or glucose-galactose malabsorption, the severity of the condition should be taken into careful consideration before prescribing Premplus or Premplus Cycle. The patients should be closely monitored.

Genitourinary

Endometriosis

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

Uterine Leiomyomata

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

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.

Hematologic

Venous thromboembolism

Available epidemiological data indicate that use of estrogen with or without progestin by postmenopausal women is associated with an increased risk of developing venous thromboembolism (VTE).

In the *estrogen plus progestin* arm of the WHI trial, among 10,000 women on combined HRT over a one-year period, there were 18 more cases of venous thromboembolism, including 8 more cases of pulmonary embolism.¹⁹

In the *estrogen-alone* arm of the WHI trial, among 10,000 women on estrogen therapy over a one-year period, there were 7 more cases of venous thromboembolism, although there was no statistically significant difference in the rate of pulmonary embolism.³²

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

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.

If feasible, estrogens with or without progestins should be discontinued at least 4 weeks before major surgery which may be associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

Hepatic/Biliary/Pancreatic

Gallbladder diseases

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

Hepatic hemangiomas

Particular caution is indicated in women with hepatic hemangiomas, as HRT may cause an exacerbation of this condition.

Jaundice

Caution is advised in patients with a history of liver and/or biliary disorders. If cholestatic jaundice develops during treatment, the treatment should be discontinued and appropriate investigations carried out.

Liver function tests

Liver function tests should be done periodically in subjects who are suspected of having hepatic disease. For information on endocrine and liver function tests, see **Monitoring and Laboratory Tests**.

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 women with hereditary angioedema.

Neurologic

Cerebrovascular insufficiency

Patients who develop visual disturbances, classical migraine, transient aphasia, paralysis or loss of consciousness should discontinue medication.

Patients with a previous history of classical migraine and who develop a recurrence or worsening of migraine symptoms should be reevaluated.

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.^{21, 33}

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).²¹

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.³³

When data from the *estrogen plus progestin* arm of the WHIMS and the *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).³³

Since this study was conducted in women aged 65-79 years, it is unknown whether these findings apply to younger postmenopausal women.

Epilepsy

Particular caution is indicated in women with epilepsy, as HRT may cause an exacerbation of this condition.

Ophthalmologic

Visual abnormalities

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

Psychiatric

Depression

Patients who are taking progestogens and have a history of depression should be observed. If the depression occurs to a serious degree, the drug should be discontinued.

Renal

Fluid retention

Estrogens with or without progestins may cause fluid retention.

Therefore, particular caution is indicated in cardiac, renal dysfunction, or asthma. If, in any of the above-mentioned conditions, a worsening of the underlying disease is diagnosed or suspected during treatment, the benefits and risks of treatment should be reassessed based on the individual case.

Special Populations

Pregnant Women: Estrogens/progestins should not be used during pregnancy.

Nursing Women: Estrogen should not be used during lactation.

Pediatrics: Clinical studies have not been conducted in the pediatric population. Premplus® and Premplus Cycle® are not indicated for use in children.

Geriatrics (> 65 years of age): There have not been sufficient numbers of geriatric women involved in clinical studies utilizing CE + MPA to determine whether those over 65 years of age differ from younger subjects in their response to CE + MPA.

The Women's Health Initiative Study

In the Women's Health Initiative (WHI) estrogen plus progestin substudy (daily conjugated estrogens 0.625 mg plus medroxyprogesterone acetate 2.5 mg), there was a higher relative risk of nonfatal stroke and invasive breast cancer in women greater than 65 years of age.

In the WHI estrogen-alone substudy (daily CE [0.625 mg] versus placebo), there was a higher relative risk of stroke in women greater than 65 years of age.

The Women's Health Initiative Memory Study

In the Women's Health Initiative Memory Study (WHIMS) of postmenopausal women 65 to 79 years of age, there was an increased risk of developing probable dementia in women receiving estrogen plus progestin or estrogen-alone when compared to placebo.

Since both ancillary studies were conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women.

Monitoring and Laboratory Tests

Before Premplus® or Premplus Cycle® is administered, the patient should have a complete physical examination including 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 three to six months of initiation of treatment to assess response to treatment. Thereafter, examinations should be made at intervals of at least once a year. Appropriate investigations should be arranged at regular intervals as determined by the physician.

Mammography examinations should be scheduled based on patient age, risk factors and prior mammogram results.

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

ADVERSE REACTIONS

Adverse Drug Reaction Overview

See **Warnings/Precautions** regarding potential induction of malignant neoplasia and other adverse effects similar to those observed with oral contraceptives.

The following adverse reactions have been reported with estrogen/progestin combination in general:

Blood and lymphatic system disorders

Altered coagulation tests (see **WARNINGS AND PRECAUTIONS**, **Drug-Laboratory Tests Interactions**).

Cardiac disorders

Palpitations; increase in blood pressure (see **WARNINGS AND PRECAUTIONS**); coronary thrombosis.

Endocrine disorders

Increased blood sugar levels; decreased glucose tolerance.

Eye disorders

Neuro-ocular lesions (e.g. retinal thrombosis, optic neuritis); visual disturbances; steepening of the corneal curvature; intolerance to contact lenses.

Gastrointestinal disorders

Nausea; vomiting; abdominal discomfort (cramps, pressure, pain, bloating).

General disorders and administration site conditions

Fatigue; changes in appetite; changes in body weight; changes in libido.

Hepatobiliary disorders

Gallbladder disorder; asymptomatic impaired liver function; cholestatic jaundice.

Musculoskeletal and connective tissue disorders

Musculoskeletal pain including leg pain not related to thromboembolic disease (usually transient, lasting 3-6 weeks) may occur.

Nervous system disorders

Aggravation of migraine episodes; headaches; dizziness; neuritis.

Psychiatric disorders

Mental depression; nervousness; irritability.

Renal and urinary disorders

Cystitis; dysuria; sodium retention; edema.

Reproductive system and breast disorders

Breakthrough bleeding; spotting; change in menstrual flow; dysmenorrhea; vaginal itching/discharge; dyspareunia; endometrial hyperplasia; pre-menstrual-like syndrome; reactivation of endometriosis; changes in cervical erosion and amount of cervical secretion; breast swelling and tenderness.

Skin and subcutaneous tissue disorders

Chloasma or melasma, which may persist when drug is discontinued; erythema multiforme; erythema nodosum; haemorrhagic eruption; loss of scalp hair; hirsutism and acne.

Vascular disorders

Isolated cases of: thrombophlebitis; thromboembolic disorders.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

A phase III double-blind, randomized study⁹ was conducted to compare the efficacy and safety of various regimens of Premarin® (conjugated estrogens) and medroxyprogesterone acetate (MPA). Efficacy was determined by the incidence of endometrial hyperplasia at the twelve month evaluation. A total of 1,724 generally healthy postmenopausal women (mean age, 54.0 years ± SD 4.6) participated in the study. The patients were considered as having completed the study if they participated in all 13 cycles (28 days/cycle). The five arms in the study were: 2 for Premplus®, 2 for Premplus Cycle®, and 1 for Premarin® alone.

Prior to treatment, the following were performed: physical examinations, vital signs, papanicolaou smear, laboratory safety screen, mammography, follicle stimulating hormone (FSH), and endometrial biopsy. During the patient visit for Cycle 6, all but the mammography

and FSH were performed. At the end of the study, Cycle 13, all but the FSH were performed.

No dose-dependent incidence of adverse experiences was seen in the multicenter efficacy and safety study. In the Premarin®/MPA groups, the most frequent treatment-emergent drug-related study event was breast pain (32% to 36%), reported by approximately one third of the patients in each of the three groups. By comparison, significantly ($p < 0.05$) fewer (12%) Premarin®-treated patients reported breast pain. Headache was the most common drug-related study event in the Premarin® alone group, reported by 69 (20%) patients, and the second most common event in the Premarin®/MPA groups (16% to 26%). Table 1 summarizes the treatment-emergent drug-related study events reported by 2% or more of the patients.

Table 1: Treatment-Emergent Drug-Related Study Events With an Incidence of $\geq 2\%$

Study Event	Premplus® 0.625 mg CE/2.5 mg MPA (n = 340)	Premplus® 0.625 mg CE/5.0 mg MPA (n = 338)	Premplus Cycle® 0.625 mg CE/10.0 mg MPA (n = 348)	Premarin® 0.625 mg CE (no MPA) (n=347)
	No. (%) of Patients ⁺			
General disorders and administration site conditions				
Asthenia	13 (4)	18 (5)	16 (5)	18 (5)
Chest pain	5 (1)	5 (1)	7 (2)	2 (<1)
Generalized edema	12 (4)	12 (4)	8 (2)	9 (3)
Edema	5 (1)	6 (2)	5 (1)	5 (1)
Peripheral edema	11 (3)	10 (3)	7 (2)	11 (3)
Pain	12 (4)	15 (4)	17 (5)	11 (3)
Vascular disorders				
Hypertension	7 (2)	7 (2)	11 (3)	7 (2)
Vasodilatation	2 (<1)	8 (2)	4 (1)	9 (3)
Gastrointestinal disorders				
Diarrhea	4 (1)	3 (<1)	11 (3)	6 (2)
Dyspepsia	5 (1)	5 (1)	7 (2)	4 (1)
Flatulence	26 (8)	27 (8) ^e	23 (7)	14 (4) ^b
Nausea	26 (8)	21 (6)	25 (7)	19 (5)
Abdominal pain	36 (11)	53 (16)	63 (18)	46 (13)
Musculoskeletal connective tissue, and bone disorders				
Leg cramps	8 (2)	11 (3)	7 (2)	8 (2)

Table 1: Treatment-Emergent Drug-Related Study Events With an Incidence of ≥ 2%

Study Event	Premplus® 0.625 mg CE/2.5 mg MPA (n = 340)	Premplus® 0.625 mg CE/5.0 mg MPA (n = 338)	Premplus Cycle® 0.625 mg CE/10.0 mg MPA (n = 348)	Premarin® 0.625 mg CE (no MPA) (n=347)
Back pain	19 (6)	16 (5)	26 (7)	13 (4)
Nervous system disorders				
Headache	69 (20)	54 (16) ^d	90 (26) ^b	69 (20)
Depression	14 (4) ^b	28 (8) ^a	22 (6)	22 (6)
Migraine	6 (2)	9 (3)	9 (3)	7 (2)
Dizziness	9 (3)	8 (2)	14 (4)	10 (3)
Emotional lability	5 (1)	6 (2)	7 (2)	4 (1)
Insomnia	7 (2)	6 (2)	9 (3)	2 (<1)
Nervousness	4 (1)	9 (3) ^c	10 (3) ^c	1 (<1) ^{b, d}
Skin and subcutaneous tissue disorders				
Acne	1 (<1)	5 (1)	7 (2)	6 (2)
Pruritus	20 (6) ^e	19 (6) ^e	15 (4)	6 (2) ^{a, b}
Rash	8 (2)	6 (2)	6 (2)	5 (1)
Reproductive system and breast disorders				
Breast enlargement	14 (4) ^c	14 (4) ^c	10 (3)	4 (1) ^{a, b}
Breast pain *	110 (32) ^c	123 (36) ^c	115 (33) ^c	40 (12) ^{a, b, d}
Cervix disorder**	10 (3)	6 (2)	12 (3)	12 (3)
Dysmenorrhea	26 (8) ^d	18 (5) ^d	46 (13) ^{a, b, c}	17 (5) ^d
Endometrial hyperplasia	2 (<1)	0 (0)	0 (0)	57 (20)
Leukorrhea	19 (6)	13 (4)	21 (6)	24 (7)
Menstrual disorder	7 (2)	1 (<1)	2 (<1)	3 (<1)
Pelvic pain	11 (3)	13 (4)	22 (6)	16 (5)
Uterine spasm	7 (2) ^e	4 (1)	8 (2) ^c	0 (0) ^{a, d}
Vaginal bleeding ***	19 (6) ^b	9 (3) ^{d, e}	22 (6) ^b	28 (8) ^b
Vaginitis	13 (4) ^c	13 (4) ^c	10 (3)	4 (1) ^{a, b}

Table 1: Treatment-Emergent Drug-Related Study Events With an Incidence of ≥ 2%

Study Event	Premplus® 0.625 mg CE/2.5 mg MPA (n = 340)	Premplus® 0.625 mg CE/5.0 mg MPA (n = 338)	Premplus Cycle® 0.625 mg CE/10.0 mg MPA (n = 348)	Premarin® 0.625 mg CE (no MPA) (n=347)
Investigations				
Pap smear abnormal†	5 (1) ^e	0 (0)	2 (<1)	0 (0) ^a
Weight increased	9 (3)	10 (3)	10 (3)	10 (3)
Psychiatric disorders				
Depression	14 (4) ^b	28 (8) ^a	22 (6)	22 (6)
Emotional lability	5 (1)	6 (2)	7 (2)	4 (1)
Nervousness	4 (1)	9 (3) ^e	10 (3) ^e	1 (<1) ^{b,d}

+ Patients were counted only once for a particular study event.

* Breast pain also includes breast discomfort, breast soreness, breast tenderness, mastodynia, nipple soreness and nipple tenderness.

** Cervix disorder includes cervical dysplasia, cervical erosion, cervical hypersecretion.

† Pap smear abnormal refers to positive Pap smear class III through V.

*** Vaginal bleeding includes menorrhagia, metrorrhagia, uterine hemorrhage, and vaginal hemorrhage.

a, b, d, e = Significant difference (p < 0.05) from treatment group Premplus® (0.625/2.5 mg), Premplus® (0.625/5.0 mg), Premplus Cycle® (0.625/10.0 mg) and Premarin® (0.625 mg) respectively.

The above table summarizes the treatment-emergent drug-related study events reported by greater than 2% of the patients. The number of patients with any study event is not necessarily the sum of the individual events since a patient might have reported two or more different study events. The addition of progestin to estrogen replacement therapy may contribute to breast pain. This is reflected by the greater percentage of patients with breast pain on combination therapy than on Premarin alone.

Less Common (<2%) Clinical Trial Adverse Drug Reactions

General disorders and administration site conditions

Fever, hypothermia, malaise, moniliasis, ulcer

Cardiac disorders

Angina pectoris, extrasystoles, palpitation, phlebitis, postural hypotension, spider angioma, tachycardia, varicose vein

Gastrointestinal disorders

Colitis, constipation, dry mouth, enterocolitis, eructation, gastritis, gingivitis, glossitis, increased appetite, mouth ulceration, periodontal abscess, rectal hemorrhage, salivary gland enlargement, stomach ulcer, taste perversion, tenesmus, thirst, tongue edema, vomiting

Endocrine disorders

Goiter, hypothyroidism, pituitary activity increased

Hepatobiliary disorders

Cholecystitis, cholelithiasis

Immune system disorders

Allergic reaction, face edema

Metabolism and nutrition disorders

Anorexia, bilirubinemia, hypercholesteremia, hyperglycemia, hyperkalemia, hyperlipemia, hypocalcemia, obesity, increased appetite

Musculoskeletal and connective tissue disorders

Arthralgia, arthritis, bursitis, myalgia, myasthenia, tenosynovitis, muscle twitching, neck pain

Neoplasms benign and malignant

Breast neoplasm, cervix neoplasm

Nervous system disorders

Abnormal dreams, agitation, amnesia, anxiety, hyperesthesia, hypoesthesia, neurosis, paresthesia, reflexes decreased, somnolence, tinnitus, thinking abnormal, tremor, vertigo

Renal and urinary tract disorders

Bladder pain, cystitis

Respiratory, thoracic and mediastinal disorders

Asthma, bronchitis, dyspnea, epistaxis, pharyngitis, pneumonia, rhinitis, sinusitis

Skin and subcutaneous tissue disorders

Contact dermatitis, dry skin, eczema, fungal dermatitis, hair discolouration, herpes simplex, herpes zoster, hirsutism, maculopapular rash, skin carcinoma, skin discoloration, skin benign neoplasm, skin hypertrophy, sweating, urticaria

Eye disorders

Abnormal vision, abnormality of accommodation, amblyopia, conjunctivitis, diplopia, dry eyes, eye haemorrhage, eye pain, lacrimation, visual field defect

Renal and urinary disorders

Hematuria, nocturia, oliguria, polyuria, urinary incontinence, urinary tract infection, urinary urgency

Reproductive system and breast disorders

Anorgasmia, breast engorgement, cervix carcinoma, endometrial carcinoma, endometrial hyperplasia, fibrocystic breast, genital edema, labial edema, mastitis, salpingitis, uterine enlargement, uterine fibroids enlarged, uterine neoplasm, vulvovaginitis

Blood and lymphatic system disorders

Anaemia, hypochromic anaemia, leucopenia, lymphocytosis, lymphadenopathy

Investigations

Fibrinolysis increased, serum glutamic oxaloacetic transaminase (SGOT) increased

Psychiatric disorders

Hostility, libido decreased, anorgasmia

Vascular disorders

Hypertension, vasodilatation, thrombophlebitis

Infections and infestations

Flu syndrome

Post-Market Adverse Drug Reactions

Enlargement of hepatic hemangiomas; angioedema, increased triglycerides; ischemic colitis, growth potentiation of benign meningioma

If adverse symptoms persist, the prescription of HRT should be re-considered.

DRUG INTERACTIONS

Overview

In vitro and in vivo studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4, such as St. John's wort (*Hypericum perforatum*) preparations, phenobarbital, phenytoin, carbamazepine, rifampicin and dexamethasone may reduce plasma concentrations estrogens, possibly resulting in a decrease in the therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4, such as cimetidine, erythromycin, ketoconazole, clarithromycin, itraconazole, ritonavir, and grapefruit juice, may increase plasma concentrations of estrogens and may result in side effects.

Data from a drug-drug interaction study involving conjugated estrogens and medroxyprogesterone acetate indicate that the pharmacokinetic disposition of both drugs are not altered when the drugs are co-administered. Other clinical drug-drug interaction studies have not been conducted with conjugated estrogens.

Estrogens may diminish the effectiveness of anticoagulant, antidiabetic and antihypertensive agents.

Preparations inducing liver enzymes (e.g. barbiturates, hydantoins, carbamazepine, meprobamates, phenylbutazone or rifampicin) may interfere with the activity of orally administered estrogens.

Drug-Drug Interactions

Aminoglutethimide administered concomitantly with MPA may significantly depress the bioavailability of MPA.

Drug-Food Interactions

CYP3A4 inhibitors such as grapefruit juice may increase plasma concentrations of 17 β -estradiol and may result in side effects.

A single dose study in healthy, postmenopausal women was conducted to investigate any potential drug interaction when 2 x 0.625 mg Premarin (conjugated estrogens) and 2.5 mg medroxyprogesterone acetate (MPA) tablets were administered immediately following a high-fat breakfast. Administration with food slowed the absorption of the conjugated estrogens, thereby reducing the C_{max} of the various estrogens by 25% to 30%, and increasing MPA C_{max} by 89% and $AUC_{0-\infty}$ by 28%. Thus, food slightly lowered the C_{max} , but did not affect the AUC, of the estrogens from a 0.625 mg Premarin tablet; food significantly increased the C_{max} and AUC of MPA from a 2.5-mg tablet.

Drug-Herb Interactions

It was found that some herbal products (e.g., St. John's wort), which are available as over-the-counter (OTC) products, might interfere with steroid metabolism, and therefore alter the efficacy and safety of estrogen/progestin products. Hot flashes and vaginal bleeding have been reported in patients taking estrogen replacement therapy (ERT) and combined estrogen plus progestin therapy (HRT) and St. John's wort. St. John's wort may induce hepatic microsomal enzymes, which theoretically may result in reduced efficacy of ERT and HRT.

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

Drug-Laboratory Test Interactions

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

- increased prothrombin time and partial thromboplastin time; increased levels of fibrinogen and fibrinogen activity, increased coagulation factors VII, VIII, IX, X; increased norepinephrine-induced platelet aggregability; decreased antithrombin III;
- impaired glucose tolerance;
- increased serum triglycerides and phospholipids concentration.
- increased thyroid-binding globulin (TBG) levels leading to increased circulating total thyroid hormone (T₄), as measured by column or radioimmunoassay; T₃ resin uptake is decreased, reflecting the elevated TBG; free T₄ concentration is unaltered.
- other binding proteins may be elevated in serum i.e., corticosteroid binding globulin (CBG), sex-hormone binding globulin (SHBG), leading to increased circulating corticosteroids and sex steroids respectively, free or biologically active hormone concentrations are unchanged;

The results of the above laboratory tests should not be considered reliable unless therapy has been discontinued for two to four weeks.

The pathologist should be informed that the patient is receiving hormone replacement therapy **(HRT) when relevant specimens are submitted.**

DOSAGE AND ADMINISTRATION

Dosing Considerations

Use of estrogens alone or in combination with progestins therapy should be limited to the shortest duration consistent with treatment goals and risks for the individual woman. Patients should be re-evaluated periodically as clinically appropriate to determine if treatment is still necessary (see boxed Serious Warnings and Precautions). For women who have intact uteri, adequate diagnostic measures, such as endometrial sampling, when indicated, should be undertaken to rule out malignancy in cases of undiagnosed persistent or recurring abnormal vaginal bleeding.

Recommended Dose and Dosage Adjustment

Premplus[®] 0.625 mg conjugated estrogens tablet and 2.5 mg medroxyprogesterone acetate (MPA) tablet and Premplus[®] 0.625 mg conjugated estrogens tablet and 5.0 mg MPA tablet, continuous therapy:

The starting dose is one maroon 0.625 mg conjugated estrogens (Premarin[®]) tablet plus one white 2.5 mg MPA tablet taken at the same time once daily for 28 days, or one maroon 0.625 mg conjugated estrogens tablet plus one purple 5.0 mg MPA tablet taken at the same time once daily every 28 days. There is no need for the patient to count days between cycles because there are no off-tablet days.

A starting dose of Premplus[®] 0.625 mg/2.5 mg is appropriate for most women entering menopause. Consider increasing the dose to the Premplus[®] 0.625 mg/5.0 mg therapy if amenorrhea is not achieved within a few months of initiating therapy. Once amenorrhea is achieved, consider dose reduction of MPA to 2.5 mg.

Additional factors, which should be taken into consideration when adjusting the dose, should include the patient's medical history, occurrence of adverse events, laboratory results and physical and gynecological examination. Patients should be re-evaluated at regular intervals.

Premplus Cycle[®] 0.625 mg conjugated estrogens tablet and 10 mg medroxyprogesterone acetate tablet, cyclic therapy:

A dose of one maroon 0.625 mg conjugated estrogens (Premarin[®]) tablet administered for 28 days at the same time each day and one peach 10 mg MPA tablet to be taken at the same time from day 15-28 of a 28-day cycle, when a cyclic regimen where a higher dose of medroxyprogesterone acetate is needed and regular withdrawal bleeding is medically appropriate on an individualized basis.

Additional factors which should be taken into consideration when adjusting the dose should include the patient's medical history, occurrence of adverse events, laboratory results and physical and gynecological examination. Patients should be re-evaluated at regular intervals.

Missed Dose

If a patient misses a dose, it should be taken as soon as possible. If it is close to the patient's next scheduled dose, the missed dose should be skipped, and the patient should continue with her normal schedule. The patient should not take two doses at the same time.

Administration

Oral

OVERDOSAGE

Symptoms of overdose:

Numerous reports of ingestion of large doses of estrogen products and estrogen-containing oral contraceptives by young children have not revealed acute serious ill effects.

Overdosage with estrogen may cause nausea, breast discomfort, fluid retention, bloating or vaginal bleeding in women. Overdosage with MPA, in female patients, may result in a period of amenorrhea of variable length and may be followed by irregular menses for several cycles. No cases of overdosage in male patients have been reported. However, such overdosage, if it were to occur, would not likely result in any particular symptomatology.

Treatment of overdose:

Symptomatic treatment should be given in the case of estrogen overdosage. There is no known therapy for overdosage of medroxyprogesterone. Doses as high as 1000 mg of medroxyprogesterone for the therapy of endometrial carcinoma have been used without adverse effect.

ACTION AND CLINICAL PHARMACOLOGY**Mechanism of Action**

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 structures⁶, 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 anovulatory cycle, estrogen is the primary determinant in the onset of menstruation.

Estrogen products act by regulating the transcription of a limited number of genes. 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 tissues of the reproductive tract, breast, pituitary, hypothalamus, liver and bone of women.

Progesterone is secreted by the ovary mainly from the corpus luteum during the second half of the menstrual cycle. Progesterone released during the luteal phase of the cycle leads to the development of a secretory endometrium. Estrogen precedes and accompanies progesterone in its action upon the endometrium and is essential to the development of the normal endometrial pattern.

Pharmacodynamics

Currently, there are no pharmacodynamic data known for CE/MPA or CE plus MPA.

Conjugated estrogens used in therapy are soluble in water and are well absorbed through the skin, mucous membranes, and gastrointestinal tract after release from the drug formulation. Like estrogens, progestogens diffuse freely into the cell nucleus where they bind to the progesterone receptor and influence the transcription of a limited set of genes. Progesterone receptors are primarily located in the female reproductive tract. Medroxyprogesterone acetate (MPA) differs considerably in its metabolic and pharmacologic effects from natural progesterone. Androgenic and anabolic effects of MPA have been noted with high doses, but the drug is apparently devoid of significant estrogenic activity.

Timing of the initiation of estrogen therapy relative to the start of menopause may affect the overall risk benefit profile. The WHI estrogen plus progestin substudy stratified by age showed in women 50-59 years of age, a non-significant trend toward reduced risk for overall mortality [HR 0.69 (95 percent CI 0.44-1.07)] when compared to the 60-69 year-old and 70-79 year-old groups with hazard ratios of 1.09 (95 percent CI 0.83-1.44) and 1.06 (95 percent CI 0.80-1.41) respectively.

Effects on vasomotor symptoms associated with estrogen deficiency

Hot flushes, feelings of intense heat over the upper trunk and face, with flushing of the skin and sweating occur in approximately 80% of women as a result of the decrease in ovarian hormones. These vasomotor symptoms are seen in women whether menopause is surgically induced or spontaneous. However, hot flushes may be more severe in women who undergo surgical menopause. Hot flushes can begin before the cessation of menses. A double-blind, randomized, parallel study has confirmed a significant reduction in hot flushes experienced by menopausal women taking Premplus[®] or Premplus Cycle[®].⁹

Effects on Osteoporosis associated with estrogen deficiency

For several years following natural or induced menopause, the rate of bone mass decline is accelerated. Conjugated estrogens reduce bone resorption and retard postmenopausal bone loss. Case-control studies have shown a reduction of up to 60% in hip and wrist fractures in women whose estrogen replacement was begun within a few years of menopause.²⁶ Studies also suggest that estrogen reduces the rate of vertebral fractures. One clinical study¹³ demonstrated that even when estrogen was started as late as fifteen years after menopause, further loss of bone mass was prevented, but was not restored to premenopausal levels. The effect on bone mass conservation is sustained only as long as conjugated estrogens therapy is continued.

Studies to date suggest that the addition of MPA to estrogen replacement therapy does not interfere with the beneficial effects of Premarin[®] on bone.¹⁷

Effects on the Endometrium

The use of unopposed estrogen therapy has been associated with an increased risk of endometrial hyperplasia, a possible precursor of endometrial adenocarcinoma^{7,8}. The results of clinical studies indicate that the addition of a progestin to an estrogen replacement regimen for more than 10 days per cycle reduces the incidence of endometrial hyperplasia and the attendant risk of adenocarcinoma in women with intact uteri. The addition of a progestin into an estrogen replacement regimen has not been shown to interfere with the efficacy of estrogen replacement therapy for its approved indications. Data from a large clinical trial indicate that MPA administered in the recommended dose to women receiving Premarin[®] 0.625 mg reduces the incidence of hyperplastic changes and hence reduces the risk of developing adenocarcinoma⁹. This is the clinical rationale for combining conjugated estrogens found in Premarin[®] tablets with MPA in product presentations of Premplus[®] and Premplus Cycle[®].

Effect on bleeding patterns

With a continuous therapy, several bleeding patterns may occur. These may range from absence of bleeding to irregular bleeding. If bleeding occurs, it is frequently light spotting or moderate bleeding. These bleeding patterns may resolve with the continued use of Premplus[®]. During a 1-year clinical trial⁹ the occurrence of bleeding or spotting was measured for the last 7 cycles of treatment with a continuous regimen of Premarin[®] and MPA. Results demonstrated that a significantly greater percentage of women taking Premarin[®] and MPA (0.625 mg/5.0 mg) continuous therapy had no bleeding or spotting compared to the Premarin[®] and MPA (0.625 mg/2.5 mg) continuous therapy.

With a cyclic therapy of Premarin[®] and MPA, it is customary to experience withdrawal bleeding or withdrawal spotting. This withdrawal bleeding or spotting may begin between day 20 of one 28-day cycle and day 5 of the next 28-day cycle. During a 1-year clinical trial⁹, the overall incidence of withdrawal bleeding (with or without spotting) or withdrawal spotting was 62.6% of cycles.

In addition to withdrawal bleeding, irregular bleeding may occur with cyclic therapy. In a 1-year clinical trial⁹, the reported mean number of days of irregular bleeding and irregular spotting for each cycle were 4.8 days and 2.5 days, respectively.

Pharmacokinetics

Coadministration of conjugated estrogens with MPA does not affect the pharmacokinetic profile of MPA; similarly, MPA does not affect the pharmacokinetic profile of the conjugated or unconjugated estrogens.

Absorption: Conjugated estrogens are soluble in water and are well absorbed through the skin, mucous membranes, and the gastrointestinal tract after release from the drug formulation. However, Premplus[®] and Premplus Cycle[®] contain a modified-release formulation of conjugated

estrogens that slowly releases estrogens over several hours. Maximum plasma concentrations of the various conjugated and unconjugated estrogens are attained within 4 to 10 hours after dose administration. MPA is rapidly absorbed from the gastrointestinal tract, and maximum MPA plasma concentrations are attained within 2 to 4 hours after dose administration.

An open-label, three period crossover study was conducted to investigate any potential pharmacokinetic interaction between Premarin® (conjugated estrogens) and MPA. Fifty-four women received single oral doses each of two 0.625 mg Premarin® tablets, two 5.0 mg MPA tablets in a capsule, and two 0.625 mg Premarin® tablets and two 5.0 mg MPA tablets in a capsule concomitantly.

The pharmacokinetic data obtained from this study is presented in Table 2, below. The data are presented for individual components of Premarin® and for MPA. The pharmacokinetic profiles of exogenous estrone and total estrone are based on plasma concentrations that are adjusted for baseline concentrations.

Table 2: Pharmacokinetic Parameters^a for Unconjugated and Conjugated Estrogens¹ and Medroxyprogesterone Acetate (2 x 0.625 mg/5.0 mg)

Drug	Treatment	PK Parameter – result and standard deviation			
		C _{max} (pg/mL)	t _{max} (hr)	AUC _T (pg·h/mL)	AUC _{0-∞} (pg·h/mL)
Unconjugated Estrogens					
estrone	Premarin	179±60	8.5±2.2	4009±1321	5700±2152
	Premarin + MPA	181±70	8.3±2.6	3978±1473	5621±2366
estrone BA*	Premarin	159±58	8.5±2.2	3065±1112	3757±1510
	Premarin + MPA	160±68	8.3±2.6	2961±1211	3618±1679
equilin	Premarin	76±29	7.8±2.8	1100±532	1327±578
	Premarin + MPA	77±35	7.2±2.3	1051±535	1289±609
Conjugated Estrogens					
total estrone	Premarin	7.01±4.16	7.0±2.0	107±59	124±72
	Premarin + MPA	7.11±4.11	7.5±2.1	108±60	126±77
total estrone BA*	Premarin	6.82±4.04	7.0±2.0	97±52	109±61
	Premarin + MPA	6.91±4.03	7.5±2.1	98±55	109±65
total equilin	Premarin	5.18±2.83	5.5±1.9	64.9±39.2	69.1±44.7
	Premarin + MPA	5.36±3.24	5.9±1.9	66.0±42.2	70.3±48.2
Medroxyprogesterone Acetate					
MPA	Premarin	33.3±1.30	2.7±1.7	49.7±16.2	58.0±16.7

Table 2: Pharmacokinetic Parameters^a for Unconjugated and Conjugated Estrogens¹ and Medroxyprogesterone Acetate (2 x 0.625 mg/5.0 mg)

Drug	Treatment	PK Parameter – result and standard deviation			
		C _{max} (pg/mL)	t _{max} (hr)	AUC _T (pg·h/mL)	AUC _{0-∞} (pg·h/mL)
	Premarin + MPA	2.84±1.02	2.6±1.7	42.2±11.7	49.4±13.0

1 Estrogen (unconjugated & conjugated) source is Premarin 0.625 mg tablets

a Values are mean ± SD

* BA = Baseline adjusted

This pharmacokinetic study was conducted to investigate potential interactions between single doses of Premarin and MPA given concomitantly. The results demonstrated that single-dose coadministration of 2 x 0.625 mg Premarin tablets with 2 x 5.0 mg MPA encapsulated tablets does not significantly affect the pharmacokinetics of estrone, equilin, total estrone, total equilin, or MPA.

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 concentrations in the sex hormone target organs. Estrogens circulate in the blood largely bound to sex hormone binding globulin (SHBG) and albumin (50-80% bound to plasma proteins). MPA is approximately 90% bound to plasma proteins but does not bind to SHBG.

Metabolism: Metabolism and inactivation of estrogens occur primarily in the liver. Metabolism and elimination of MPA occurs primarily in the liver via hydroxylation, with subsequent conjugation and elimination in the urine.

Excretion: Some estrogens are excreted in bile; however, they are reabsorbed from the intestine and returned to the liver through the portal venous system.

Estradiol, estrone, and estriol are excreted in the urine along with glucuronide and sulfate conjugates. Most metabolites of MPA are excreted as glucuronide conjugates with only minor amounts excreted as sulfates.

The apparent terminal-phase disposition half-life (t_{1/2}) of the various estrogens is prolonged by the slow absorption from Premarin[®]/MPA and ranges from 10 to 24 hours. MPA has a mean t_{1/2} of 38 hours.

Special Populations and Conditions

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

Estrogen pharmacology

Endogenous estrogens are largely responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is substantially more potent than its metabolites, estrone and estriol, at the receptor level.

The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70 to 500 mcg of estradiol daily, depending on the phase of the menstrual cycle. After menopause, most endogenous estrogen is produced by conversion of androstenedione, secreted by the adrenal cortex, to estrone by peripheral tissues. Thus, estrone and the sulfate-conjugated form, estrone sulfate, are the most abundant circulating estrogens in postmenopausal women.

Estrogens act through binding to nuclear receptors in estrogen-responsive tissues. To date, two estrogen receptors have been identified. These vary in proportion from tissue to tissue.

Circulating estrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone (LH) and follicle stimulating hormone (FSH) through a negative feedback mechanism. Estrogens act to reduce the elevated levels of these gonadotropins seen in postmenopausal women.

Progestin pharmacology

Parenterally administered medroxyprogesterone acetate (MPA) inhibits gonadotropin production, which in turn prevents follicular maturation and ovulation, although available data indicate that this does not occur when the usually recommended oral dosage is given as single daily doses. MPA may achieve its beneficial effect on the endometrium in part by decreasing nuclear estrogen receptors and suppression of epithelial DNA synthesis in endometrial tissue. Androgenic and anabolic effects of MPA have been noted, but the drug is apparently devoid of significant estrogenic activity.

The purpose of adding a progestin medication to long-term estrogen therapy is to reduce the risk of endometrial hyperplasia in women with intact uteri.

STORAGE AND STABILITY

Store at 15°C - 25°C.
Keep out of reach of children.

SPECIAL HANDLING INSTRUCTIONS

None required.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Premplus[®] is available in two strengths:

0.625 and 2.5 mg - two blister cards in a carton totalling 56 oral tablets.

Each card contains 14 oval, maroon CE (Premarin[®]) 0.625 mg tablets branded “0.625” on one side in white ink, and 14 oval, white MPA 2.5 mg tablets, scored on one side; debossed with two opposing “C”s on the other side.

0.625 and 5.0 mg - two blister cards in a carton totalling 56 oral tablets.

Each card contains 14 oval, maroon CE (Premarin[®]) 0.625 mg tablets branded “0.625” on one side in white ink, and 14 oval purple MPA 5.0 mg tablets, scored on one side; debossed with two “C”s on the other side.

Premplus Cycle[®] is available in one strength as follows:

0.625 mg and 10 mg - two blister cards in a carton totalling 42 oral tablets.

The **first** card contains 14 oval, maroon CE (Premarin[®]) 0.625 mg tablets branded “0.625” in white ink. The **second** blister card contains 14 oval, maroon CE 0.625 mg tablets branded, “0.625” in white ink, and 14 oval, peach MPA 10 mg tablets, scored on one side; debossed with two opposing “C”s on the other side.

Each maroon CE tablet contains 0.625 mg CE.

Each MPA tablet contains either 2.5 mg, 5 mg or 10 mg MPA.

Non-Medicinal Ingredients:

Maroon CE tablet contains the following inactive ingredients: calcium sulfate, carnauba wax, edible ink, erythrosine aluminum lake, FD&C blue No. 2, FD&C yellow No. 6, glyceryl monooleate, lactose, magnesium stearate, methyl cellulose, microcrystalline cellulose, pharmaceutical glaze, polyethylene glycol, povidone, sodium benzoate, stearic acid, sucrose, and titanium dioxide.

White MPA tablet contains the following inactive ingredients: lactose, microcrystalline cellulose, methylcellulose, and magnesium stearate.

Purple MPA tablet contains the following inactive ingredients: lactose, microcrystalline cellulose, methyl cellulose, magnesium stearate, D&C blue No. 1 aluminum lake and D&C red No. 30 aluminum lake.

Peach MPA tablet contains the following inactive ingredients: lactose, microcrystalline cellulose, methyl cellulose, magnesium stearate, D&C yellow No. 10 lake and D&C red No. 30 aluminum lake.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Conjugated estrogens, C.S.D.

Chemical name: Not applicable

Molecular formula and molecular mass: Not applicable

Structural formula: Not applicable

Description: Conjugated estrogens C.S.D. contains 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, equilenin, 17 α -dihydroequilenin, 17 β -dihydroequilin, 17 β -dihydroequilenin, 17-estradiol and δ 8,9-dehydroestrone as salts of their sulfate esters.

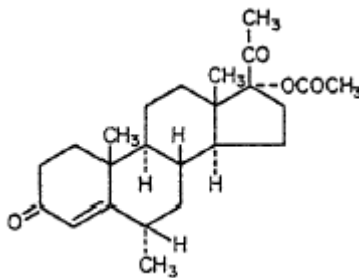
Drug Substance

Proper name: Medroxyprogesterone Acetate, USP

Chemical name: 1) Pregn-4-ene-3, 20-dione, 17-(acetyloxy)-6-methyl-, (6a)-;
2) 17-Hydroxy-6-methylpregn-4-ene-3, 20-dione acetate.

Molecular formula and molecular mass: Molecular formula is C₂₄H₃₄O₄
Molecular mass is 386.53

Structural formula:



Physicochemical properties: Medroxyprogesterone acetate is a derivative of progesterone. It is a white to off-white, odourless, crystalline powder, stable in air, melting between 200°C

and 210°C. It is freely soluble in chloroform, soluble in acetone and in dioxane, sparingly soluble in alcohol and in methanol, slightly soluble in ether, and insoluble in water.

CLINICAL TRIALS

Published Studies

Vasomotor Symptoms

The Postmenopausal Estrogen Progestin Interventions (PEPI) Trial³⁷ was a randomized clinical trial (RCT) in 875 postmenopausal women ages 45 to 64 years of age. Vasomotor symptoms were evaluated using a self-reported checklist at baseline, at 1 year, and at 3 years. The five treatment groups received either conjugated equine estrogens (CEE) 0.625 mg/day, CEE 0.625 mg/day plus cyclical (12 days per cycle) medroxyprogesterone acetate (MPA) 10 mg, CEE 0.625 mg/day plus MPA 2.5 mg/day, CEE 0.625 mg/day plus cyclical (12 days per cycle) micronized progesterone (MP) 200 mg, or placebo.

Key observations demonstrated that therapy with CEE alone and CEE with MPA and CEE with MP decreased levels of vasomotor symptoms in subjects over 36 months. On average there were no significant differences in symptom levels between each group.

At year 1, the adjusted odds of having higher vasomotor symptoms for continuous CEE with MPA vs. placebo were 0.17 (0.09, 0.32). At year 3, the adjusted odds for continuous CEE with MPA vs. placebo were 0.39 (0.22, 0.69). These reported results are the odds ratios with 95% confidence intervals from generalized Wald tests in parentheses.

Vasomotor Symptoms and Vaginal Atrophy

The Women's Health, Osteoporosis, Progestin, Estrogen (HOPE) Study³⁸ was an RCT to evaluate the safety and efficacy of lower doses of CEE and MPA in postmenopausal women. The design included a one year basic study to evaluate the efficacy of lower doses of CEE with and without MPA in relieving vasomotor symptoms (VMS) and vulvar and vaginal atrophy (VVA). A total of 2,673 healthy, postmenopausal women 40 to 65 years of age with an intact uterus (mean age of 53.3 years), including a vasomotor symptom efficacy-evaluable population (n=241 at baseline) participated.

Efficacy measures were frequency and severity of daily hot flashes and Papanicolaou smear with vaginal maturation index (VMI) to assess vaginal atrophy.

There were a total of eight treatment arms consisting of the following:
CEE 0.625 mg/day; CEE 0.625 mg/MPA 2.5 mg/day; CEE 0.45 mg/day; CEE 0.45 mg/MPA 2.5 mg/day; CEE 0.45 mg/MPA 1.5 mg/day; CEE 0.3 mg/day; CEE 0.3 mg/MPA 1.5 mg/day; or placebo.

Key observations for VMS: All active treatment groups significantly reduced mean number of hot flushes from baseline by week 1 or 2 ($P<0.01$) and all active treatment groups significantly reduced mean number of hot flushes compared with placebo by week 2 or 3 ($P<0.001$).

Numbers of hot flushes

- For the placebo group, the mean daily number of hot flushes dropped from approximately 10 at week 1, to approximately 5 at week 12, and continuing at approximately 5 to cycle 13.
- For the 0.625 mg CEE/2.5 mg MPA treatment group, the mean daily number of hot flushes decreased from approximately 10 at week 1, to approximately 1 at week 12, dropping to approximately 0.5 at cycle 13. The difference from placebo was significant ($P<0.5$) beginning from week 2 to the end of cycle 13.

Severity of hot flushes

A mild hot flush was rated a 1, a moderate hot flush a 2, and a severe hot flush a 3.

- For the placebo group, the mean daily severity of hot flushes decreased from approximately 2.1 at week 1, to approximately 1.7 at week 12, and continuing at approximately 1.7 to cycle 13.
- For the 0.625 mg CEE/2.5 mg MPA treatment group, the mean daily severity of hot flushes decreased from 2.1 at week 1, to approximately 0.5 at week 12, and dropping to approximately 0.2 at cycle 13. The difference from placebo was significant ($P<0.5$) beginning from week 2 to the end of cycle 13.

Key observations for VVA: All active treatment groups significantly increased the percentage of superficial cells from baseline at cycles 6 and 13 ($P<0.001$) and all active treatment groups significantly increased the percentage of superficial cells compared with placebo at cycles 6 and 13 ($P<0.001$).

Osteoporosis – Bone Mineral Density

The PEPI Trial¹⁷ was a RCT in 875 postmenopausal women ages 45 to 64 years of age. This study was designed to assess the effects of CEE alone in comparison with CEE and MPA or MP on bone mineral density (BMD) at the spine and the hip as measured by dual-energy x-ray absorptometry (DXA) technology. Its primary measures were BMD scores at baseline, 12 months and 36 months. Five treatment groups received either CEE 0.625 mg/day, CEE 0.625 mg/day plus cyclical (12 days per cycle) MPA 10 mg, CEE 0.625 mg/day plus MPA 2.5 mg/day, CEE 0.625 mg/day plus cyclical (12 days per cycle) MP 200 mg, or placebo.

Key observations: Women in the placebo group lost significant amounts of BMD at both the spine and the hip compared with active treatments by month 12. All active treatment groups produced significant BMD gains at the spine and hip from baseline by month 12 continuing until month 36 compared with losses in the placebo group. At 36 months, the placebo group had lost an average of 1.8% of spine BMD, and 1.7% of hip BMD, while the active treatment groups gained from 3.5% to 5.0% mean total increases in spinal BMD and a mean total increase of 1.7% hip BMD.

The Women's HOPE Study³⁹ evaluated 822 healthy, postmenopausal women (mean age of 51.6 years) with a modified intent-to-treat population (n=695 at baseline) in a 2 year, randomized, double-blind, placebo controlled osteoporosis substudy.

The efficacy measures were changes in BMD of the lumbar spine (L2 to L4) and total hip, BMC of the total body as measured by DXA, and the two biochemical markers of bone turnover, osteocalcin and N-telopeptides of type I collagen.

There were a total of 8 treatment arms consisting of the following: CEE 0.625 mg/day; CEE 0.625 mg/MPA 2.5 mg/day; CEE 0.45 mg/day; CEE 0.45 mg/MPA 2.5 mg/day; CEE 0.45 mg/MPA 1.5 mg/day; CEE 0.3 mg/day; CEE 0.3 mg/MPA 1.5 mg/day; or placebo.

Key observations: Women in the placebo group experienced significant losses ($P<0.001$) in BMD at the spine compared with baseline at the 24 month visit. All dose formulations of CEE and CEE/MPA were effective in preventing bone loss at the spine and hip from baseline ($P<0.001$) and all were effective in reducing bone turnover from baseline ($P<0.001$).

The secondary analysis of the Women's HOPE study⁴⁰ defined bone response to treatment. Response was defined as loss of $>2\%$, $<2\%$ loss, or greater than or equal to 0% gain of spine or hip BMD from baseline at months 12 and 24.

The key findings were as follows:

- At 24 months, less than 15.5% of women failed to respond to active treatment (losing $>2\%$ in spine BMD) compared with 55.2% in the placebo group.
- At 24 months, less than 15% of women failed to respond to active treatment (losing $>2\%$ in hip BMD) compared with 36.5% in the placebo group
- Women who responded to treatment had a significantly greater reduction in markers of bone turnover (osteocalcin & N-telopeptides) at 12 months ($P<0.0001$ & $P=0.0018$, respectively) and at 24 months for both markers ($P<0.0001$) than women who did not respond to treatment.

Efficacy and Safety Studies

Study demographics and trial design

A phase III double-blind, randomized study was conducted to compare the efficacy and safety of various regimens of Premarin® and medroxyprogesterone acetate (MPA). Efficacy was determined by the incidence of endometrial hyperplasia at the twelve month evaluation. Patients in all five treatment groups took 0.625 mg of Premarin® every day of a 28-day cycle; in four groups, they also took MPA (see Table 3 below).⁹

A total of 1,724 generally healthy postmenopausal women between the ages of 43 and 66 years were admitted to the study. They were eligible to participate in the study if they had their last natural menstrual cycle at least 12 months before entering the study (baseline screening). The serum screening follicle-stimulating hormone (FSH) concentrations had to be higher than the lower limit for postmenopausal women for the given laboratory. The women were relatively

healthy and had intact reproductive organs.⁹

The study was comprised of five arms: 2 for Premplus®, 2 for Premplus Cycle®, and 1 for Premarin alone, as indicated below. Each patient was to participate for 13 cycles (28 days/cycle). A total of 1,361 patients completed the study.

Table 3: Pivotal Trial Treatment Groups

Treatment Group	Strengths (mg)		Days of Use/Cycle
	Premarin	MPA	
A	0.625	2.5	1-28
B	0.625	5.0	1-28
C*	0.625	Placebo	1-14
	0.625	5.0	15-28
D*	0.625	Placebo	1-14
	0.625	10.0	15-28
E	0.625	Placebo	1-28

* results from these two non-commercialized product presentations have not been included in the “Study results” section.

Study results

Effects on the Endometrium

Table 4 summarizes the incidence of endometrial hyperplasia after one year of treatment⁹ with the continuous (28 days/cycle of both the CE and MPA tablets) therapy.

Table 4: Incidence of Endometrial Hyperplasia after One Year of Treatment

Patient	Dose Groups.....		
	Premarin®/MPA 0.625 mg/2.5 mg	Premarin®/MPA 0.625 mg/5.0 mg	Premarin® 0.625 mg
Total number of patients	279	274	283
No. (%) of patients with abnormal biopsies			
• all focal and non-focal hyperplasia	2(<1)*	0(0)*	57(20)

*Significant (p<0.001) in comparison with Premarin alone (0.625 mg).

Premarin 0.625 mg tablets contain 0.625 mg CE per tablet.

The comparator, Premarin 0.625 mg tablets, is available on the Canadian market.

Table 5 summarizes the incidence of endometrial hyperplasia after one year of treatment⁹ with conjugated estrogen/medroxyprogesterone acetate, cyclic therapy (MPA tablets taken concomitantly with Premarin tablets only on days 15 to 28).

Table 5: Incidence of Endometrial Hyperplasia after One Year of Treatment

PatientDose Groups.....	
	Premarin®/MPA 0.625 mg/10 mg	Premarin® 0.625 mg
Total number of patients	272	283
No. (%) of patients with abnormal biopsies		
• all focal and non-focal hyperplasia	0(0)*	57(20)

*Significant (p<0.001) in comparison with Premarin alone (0.625 mg).

Women treated with Premarin and MPA had a significantly (p < 0.001) lower incidence of endometrial hyperplasia than women treated with Premarin alone.

Effect on bleeding patterns:

Table 6 presents the incidence of amenorrhea for cycles 7 through 13, of the patient group who completed the study with a continuous regimen of conjugated estrogen/medroxyprogesterone acetate.

Table 6: Incidence of Amenorrhea for Cycles 7 through 13

Population	Percent (Number/Total Number) of Patients	
	----- Dose Groups -----	
	Premarin/MPA 0.625 mg/2.5 mg	Premarin/MPA 0.625 mg/5.0 mg
Completed 13 cycles	40.4% (82/203)	52.6%* (101/192)

* Significantly (p<0.05) different in comparison to the 2.5 mg regimen of Premarin/MPA continuous.

Withdrawals from the clinical study:

Safety-related events were the most common primary reasons for withdrawal from the clinical study except in the group treated with Premarin 0.625 mg CE/10 mg MPA, in which patient request predominated. The reasons for patient withdrawal and the number of patients withdrawn for each of these reasons are shown in Table 7, below.

Table 7: Summary of reasons for withdrawals from clinical study

Study Drug	# patients	-----Number of Patients (%)-----						
		Safety-Related Reasons	Failed to Return	Other Medical Event	Other Non-medical Event	Patient Request	Prestudy Screen or Protocol Violation	Lack Of Efficacy ^a
0.625 mg for 28 days in each group:								
2.5 mg MPA/28 days	340	20 (6)	6 (2)	5 (1)	5 (1)	12 (4)	10 (3)	1 (<1)
5.0 mg MPA/28 days	338	19 (6)	8 (2)	8 (2)	4 (1)	10 (3)	10 (3)	2 (<1)
10 mg MPA/14 days	348	24 (7)	6 (2)	8 (2)	7 (2)	27(8)	6 (2)	1 (<1)
No MPA	347	42 (12)	6 (2)	14 (4)	1 (<1)	15 (4)	14 (4)	0

a: Interpreted by the investigator as lack of symptom control

DETAILED PHARMACOLOGY

See “Action and Clinical Pharmacology” Section under the Health Professional Information Section.

TOXICOLOGY

Acute and long-term toxicity studies have been conducted with conjugated estrogens (Premarin[®]) plus medroxyprogesterone acetate (MPA).

Acute Toxicity

Premarin[®] plus MPA

In studies conducted by Wyeth, Premarin (125 mg/kg) was administered alone or with MPA (1000 mg/kg). In both cases, the LD₅₀ value for Premarin administered orally or intraperitoneally to male and female CD-1 mice and CD rats was greater than 125 mg/kg and the LD₅₀ value for Premarin plus MPA was greater than 125 mg + 1000 mg per kg respectively.

Sub-Acute and Chronic Toxicology

Dose Range-finding Studies

Rat

Single and multiple oral (gavage) dose range-finding studies of Premarin[®] plus MPA were performed in CD rats to establish appropriate dosages for a subsequent 3-month toxicity study. Dosages ranged from 0.025 mg + 0.2 mg to 48 mg + 384 mg per kg respectively. No drug-related mortality occurred in either study. Drug-related reduction in food consumption and decreased weight gain was noted in males at dosages ranging from 0.025 mg + 0.2 mg to 1.0 + 8.0 mg per kg in the multiple dose range finding study.

Dog

Premarin[®] plus MPA was administered orally via capsule to male and female beagle dogs in single and multiple dose range finding studies to determine drug effects and to establish appropriate dosages for a subsequent three month toxicity study. Dosages ranged from 0.025 mg + 0.2 mg to 20 mg + 160 mg per kg. No mortality occurred in either study. No drug effects other than occasional loose or mucoid feces and emesis were noted in the multiple dose range finding study.

Long-Term Toxicity

Premarin/MPA

Rat

Premarin was administered orally with MPA once daily by gavage to 9-week-old (at study initiation) male and female Charles River CD albino rats (20 per sex per group). This study was conducted by Wyeth. Dosages of 0.025 mg + 0.2 mg, 0.25 mg + 2.0 mg, and 0.5 mg + 4.0 mg per kg per day were given for 3 months. The effects (primary or secondary) of treatment occurred generally at higher concentrations of Premarin/MPA and included decreases in white blood cell count and cholesterol, increases in fibrinogen and triglycerides, decreases in food consumption, a decrease in body weight gain, a decrease in adrenal weights, a decrease in organ weights (prostate, seminal vesicle and testes, ovary and uterus), as well as increased pituitary weight in males and decreased pituitary weight in females.

The drug-induced weight changes seen in many endocrine organs were associated histologically with atrophy, hyperplasia, and sometimes mild inflammation (prostate). All of these changes also occurred in rats receiving either Premarin or MPA alone and are expected effects based on pharmacologic activity. In this 3-month study, no glucose or pancreatic changes were seen.

Dog

In a 3-month dog oral toxicity study conducted by Wyeth, Premarin plus MPA was administered via capsule to beagles, 43 to 47 weeks old (3 per sex per group) at dosages of 0.025 mg + 0.2 mg, 0.25 mg + 2.0 mg, and 0.5 mg + 4.0 mg per kg. Changes in hematologic, clinical chemistry, and urinalysis parameters were generally slight and included a decrease in erythroid values, chloride values, and urine specific gravity, as well as increased variation in erythrocyte morphology, fibrinogen values, cholesterol values, triglyceride values, protein values, and albumin values.

Changes in macroscopic and microscopic pathology included vacuoles containing glycogen in liver, adrenal cortical, prostatic and testicular atrophy and aspermatogenesis, hyperplasia of mammary glands and of the endometrium, as well as thinning of the cervical and vaginal epithelium.

All of the observed effects with Premarin plus MPA had also occurred in these two species, the rat, and the dog, when tested with Premarin or MPA separately at dosages of 0.5 mg/kg or 4.0

mg/kg, respectively. The effects were consistent with the anticipated pharmacologic effects of Premarin or MPA.

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PART III: CONSUMER INFORMATION

Premplus®
conjugated estrogens tablets CSD and
medroxyprogesterone acetate tablets USP
(Continuous therapy)

Premplus Cycle®
conjugated estrogens tablets CSD and
medroxyprogesterone acetate tablets USP
(Cyclic therapy)

IMPORTANT: PLEASE READ

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

ABOUT THIS MEDICATION**What the medication is used for::**

- To relieve menopausal and post-menopausal symptoms (vasomotor symptoms like hot flashes and night sweats):
- To prevent osteoporosis caused by low estrogen levels associated with menopause. Osteoporosis is a thinning of the bones that makes them weaker and easier to break.

Use of Premplus® or Premplus Cycle® is to be considered in light of other available therapies for the prevention of postmenopausal osteoporosis. Adequate diet, calcium and vitamin D intake, cessation of smoking as well as regular physical weight bearing exercise should be discussed with your doctor or pharmacist in addition to the administration of Premplus® or Premplus Cycle®.

Use of Premplus® tablets or Premplus Cycle® tablets for the prevention of osteoporosis is recommended only for women who are at risk of developing this condition. If you use Premplus® or Premplus Cycle® only to prevent osteoporosis from menopause, talk with your healthcare provider about whether a different treatment or medicine without estrogens might be better for you.

- To treat vulva and vaginal atrophy associated with menopause (itching, burning, dryness in or around the vagina, difficulty or burning on urination)

If you use Premplus® tablets or Premplus Cycle® tablets only to treat symptoms of vulvar and vaginal atrophy associated with menopause, talk with your healthcare provider about whether a vaginal (topical) treatment might be better for you.

Premplus® or Premplus Cycle® 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 taking Premplus® or Premplus Cycle®, women are using a combination of two hormones, an estrogen (i.e. conjugated equine estrogens tablets) and a progestin (i.e. medroxyprogesterone acetate tablets). Premplus® and Premplus Cycle® replace the hormones in your body, which naturally decrease at menopause.

Premplus® and Premplus Cycle® have been shown to provide the benefits of estrogen replacement therapy while lowering the frequency of a possible precancerous condition of the uterine lining with the addition of the progestin. This therapy is not intended for women who have had a hysterectomy (surgical removal of the uterus).

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

When a woman is between 45 and 55 years old, the ovaries normally stop making estrogens. This leads to a drop in body estrogen levels and marks the beginning of menopause or the "change of life" (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 get very uncomfortable symptoms, such as feelings of warmth in the face, neck and chest, or sudden strong feelings of heat and sweating ("hot flashes" or "hot flushes"). In some women the symptoms are mild, and they will not need to take estrogens. In other women, symptoms can be more severe. These symptoms may last only a few months or longer. Taking Premplus® or Premplus Cycle® can alleviate these symptoms. You and your healthcare provider should talk regularly about whether you still need treatment with Premplus® or Premplus Cycle®.

After menopause, some women develop osteoporosis. This is a thinning of the bones that makes them weaker and allows them to break more easily, often leading to fractures of the vertebrae, hip and wrist bones.

When it should not be used:

Estrogens and progestins should not be used to prevent heart disease, heart attacks, or strokes. You and your healthcare provider should talk regularly about the duration of your treatment with Premplus® or Premplus Cycle®.

Before using Premplus® or Premplus Cycle® be sure to tell your doctor if you have any of the following medical problems, as Premplus® or Premplus Cycle® should not be used under these conditions:

- **Known, suspected, or past history of breast cancer.**
- **Known or suspected hormone-dependent cancer.**
Estrogens may increase the chances of getting certain types of cancers, including cancer of the breast or uterus. If you have or had cancer, talk with your healthcare provider about whether you should take Premplus® or Premplus Cycle®.
- **Unexpected or unusual vaginal bleeding**
- **Have (or have had) blood clot disorders, including blood clots in the legs or lungs or thrombophlebitis (inflammation of the veins).**
- **Serious liver disease**
- **Active or past history of heart disease, heart attacks or stroke.**
- **If you are allergic to Premplus® or Premplus Cycle® or any of their ingredients, or have had any unusual reactions to their ingredients (see What the medicinal ingredients are and What the nonmedicinal ingredients are).**
- **If you are pregnant or suspect you may be pregnant.**
Since pregnancy may be possible early in the pre-menopause while you are still having spontaneous periods, the use of non-hormonal birth control should be discussed with your physician at this time. If you accidentally take estrogen during pregnancy, there is a small risk of your unborn child having birth defects.
- If you have partially or completely lost vision due to blood vessel disease of the eye.
- If you have overgrowth of the lining of the uterus.
- Have some types of congenital coagulation abnormalities (e.g. protein C, protein S, antithrombin deficiency, or anti-cardiolipin antibodies)
- If you experience migraines with aura

What the medicinal ingredients are:

Conjugated equine estrogens and medroxyprogesterone acetate.

What the nonmedicinal ingredients are:

Non-Medicinal Ingredients of Premplus® and Premplus Cycle®
Each Conjugated Estrogens Tablet contains the following inactive ingredients: calcium sulfate, carnauba wax, edible ink, erythrosine aluminum lake, FD&C blue No. 2, FD&C yellow No. 6, glyceryl monooleate, lactose, magnesium stearate, methyl cellulose, microcrystalline cellulose, pharmaceutical glaze, polyethylene glycol, povidone, sodium benzoate, stearic acid, sucrose, and titanium dioxide.

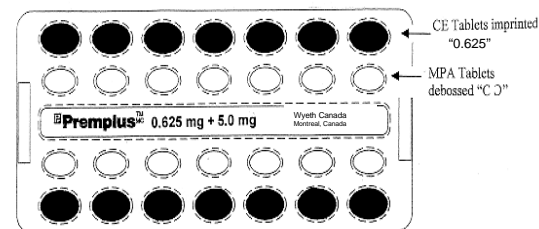
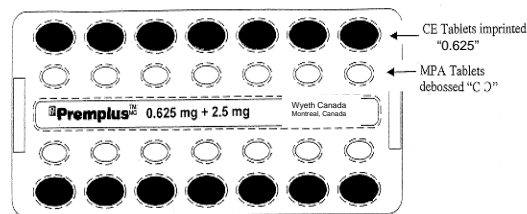
Each Medroxyprogesterone Acetate Tablet contains the following inactive ingredients:

Lactose, microcrystalline cellulose, methylcellulose and magnesium stearate. In addition, each Medroxyprogesterone Acetate 5.0 mg Tablet contains D&C blue No. 1 aluminum lake and D&C red No. 30 aluminum lake; and each Medroxyprogesterone Acetate 10.0 mg tablet contains D&C yellow No. 10 lake and D&C red No. 30 aluminum lake.

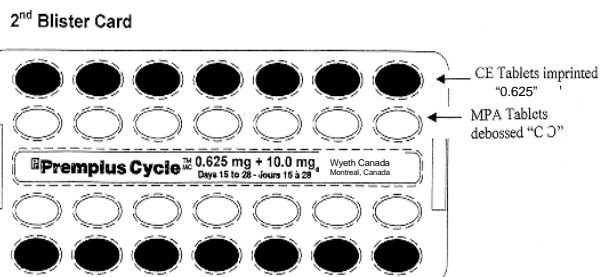
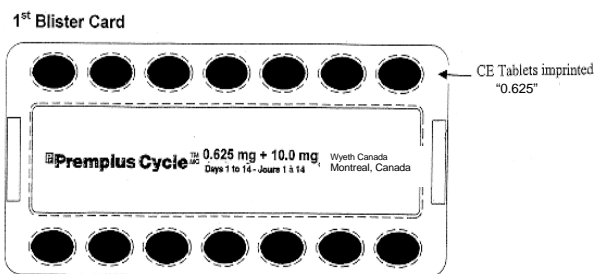
What dosage forms it comes in:

Premplus® is available as tablets, as follows:

Premplus®: conjugated estrogens tablets, 0.625 mg, and medroxyprogesterone acetate tablets, 2.5 mg, and 5.0 mg



Premplus Cycle®: conjugated estrogens tablets, 0.625 mg, and medroxyprogesterone acetate tablets, 10.0 mg



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 with or without progestins 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).

The purpose of adding a progestin medication to estrogen therapy is 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 postmenopausal 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 postmenopausal women age 65 and over with prior hysterectomy taking oral *estrogen-alone* compared to women taking placebo.

BEFORE you use Premplus® and Premplus Cycle® 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, 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 a history of high cholesterol or high triglycerides
- are pregnant or may be pregnant
- have had a hysterectomy (surgical removal of the uterus)
- smoke

Other existing conditions you should discuss with your health professional include lupus, very low calcium levels, thyroid problems, fluid retention, gallbladder disease, depression, and breastfeeding. If you have upcoming surgery or prolonged bedrest, you should also discuss these.

Clinical studies have not been conducted in the pediatric population. Premplus® and Premplus Cycle® are not indicated for use in children.

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 (such as St. John's wort). Some medications (such as medications for high blood pressure, diabetes, blood clots, sleeping, anxiety, seizures, pain-relief and tuberculosis) may affect how Premplus® and Premplus Cycle® work. Premplus® and Premplus Cycle® may also affect how other medicines work.

PROPER USE OF THIS MEDICATION

Usual dose:

Premplus® - take by mouth one maroon tablet (conjugated estrogens) and one white or purple tablet (progestin) at the same time each day, depending on the strength of the progestin you were prescribed.

Premplus Cycle® - take by mouth one maroon tablet (conjugated estrogens) at the same time each day of each month and one peach tablet (progestin) for the last 14 days of each month, i.e., days 15 to 28 of the cycle.

Estrogens should be used at the lowest dose possible for your treatment only as long as needed. You and your healthcare provider should talk regularly (for example, every 3 to 6 months) about the dose you are taking and whether you still need treatment with Premplus® or Premplus Cycle®.

Take Premplus® or Premplus Cycle® only as directed by your doctor or pharmacist.

Overdose:

Contact your physician or local Poison Control Center in case of accidental ingestion of high doses of Premplus® or Premplus Cycle®.

Overdosage with Premplus® or Premplus Cycle® may cause nausea and vomiting, breast discomfort, fluid retention, bloating, or vaginal bleeding.

Overdosage may result in a period of amenorrhea (lack of menses) of a variable length and may be followed by irregular menses for several cycles. No cases of overdosage in male patients have been reported.

Missed Dose:

If you miss a dose, take it as soon as possible. If it is almost time for your next dose, skip the missed dose and go back to your normal schedule. Do not take 2 doses at the same time.

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not take Premplus® or Premplus Cycle® for conditions for which they were not prescribed. Do not give Premplus® or Premplus Cycle® to other people, even if they have the same symptoms you have. It may harm them.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Possible side effects may include, but are not necessarily limited to, those listed in this section.

In clinical trials for Premplus® and Premplus Cycle®, lasting 13 cycles, in which 1,724 patients participated, the most common adverse effects experienced by the participants are listed below. The adverse effects are ordered by frequency (percentage of participants experiencing adverse effect):

For the patients taking Premplus® and Premplus Cycle® in the study, the most frequent side effect was breast pain, reported by approximately one third of the patients. Headache was the second most common event for these patients. The most common side effects from the study are listed below, along with the frequencies.

- Breast pain – 32 to 36%
- Headache – 16 to 26%
- Abdominal pain – 11 to 16%
- Flatulence – 7 to 8%
- Nausea – 6 to 8%
- Painful menstrual cramps – 5 to 13%
- Back pain – 5 to 7%
- Depression – 4 to 8%
- Itching of the skin – 4 to 6%
- Genital bleeding/spotting – 3 to 6%
- Weight gain – 3%

Patients may have reported two or more different side effects during the study. The addition of progestin to estrogen replacement therapy may contribute to breast pain as a greater percentage of patients on Premplus® and Premplus Cycle® reported breast pain than those on Premarin alone. The following self-limiting side effects, in the table below, are listed by frequency and body categories. These include side effects from the clinical study as well as those gathered during the marketing of Premplus® and Premplus Cycle®:

- Very Common: ≥10%
- Common: ≥1% and <10%
- Uncommon: ≥0.1% and <1%
- Rare: ≥0.01% and <0.1%
- Very rare: <0.01%

Body System	Side effects
<i>Reproductive system and breast disorders</i>	
Very common	Breast pain
Common	Breakthrough bleeding/ painful periods; spotting
Uncommon	Change in menstrual flow;
Rare	A spontaneous flow of milk from the nipple

<i>Gastrointestinal disorders</i>	
Uncommon	Nausea; bloating; abdominal pain
Rare	Vomiting, inflammation of the colon
<i>Nervous system disorders</i>	
Uncommon	Dizziness; headache (including migraine)
Rare	Enlargement of benign brain tumours
<i>Musculoskeletal, connective tissue and bone disorders</i>	
Common	Joint pain
<i>Psychiatric disorders</i>	
Uncommon	Changes in libido; mood disturbances
Rare	Irritability
<i>Skin and subcutaneous tissue disorders</i>	
Uncommon	Acne; hair loss; itching
Rare	Rash
Very rare	Tender red nodules on the shins and legs
<i>Infections and Infestations</i>	
Common	Inflammation of the vagina
<i>Immune system disorders</i>	
Rare	Hives
<i>Respiratory, thoracic and mediastinal disorders</i>	
Rare	Worsening of asthma
<i>Investigations</i>	
Common	Changes in weight (increase or decrease)
Very rare	Increase in blood pressure

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

Frequency (common or uncommon)	Symptom / possible side effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Uncommon	Abdominal pain, nausea or vomiting	✓		
Rare	Breast lump, unusual discharge		✓	
Rare	Shortness of breath, weakness, unusual fatigue, cold sweat, dizziness, sleep disturbance, indigestion, anxiety		✓	
Uncommon	Pain or swelling in the leg			✓
Common	Persistent sad mood		✓	

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

		Talk with your doctor or pharmacist		
Rare	Sharp pain in the chest, coughing blood or sudden shortness of breath			✓
Very rare	Sudden partial or complete loss of vision			✓
Rare	Sudden severe headache or worsening of headache, vomiting, dizziness, fainting, disturbance of vision or speech or weakness or numbness in an arm or leg			✓
Very rare	Unexpected vaginal bleeding, difficult/painful urination		✓	
Very rare	Yellowing of the skin or eyes		✓	
Uncommon	Memory loss, poor concentration, problems learning new ideas or skills		✓	

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

HOW TO STORE IT

Store Premplus® and Premplus Cycle® at 15° C to 25° C (room temperature).

Keep out of reach of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
 - Fax toll-free to 1-866-678-6789, or
 - Mail to:
 - Canada Vigilance Program
 - Health Canada
 - Postal Locator 0701D
 - Ottawa, Ontario
 - K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. 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 by contacting the sponsor,

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

toll-free, at: 1-800-463-6001

or at www.pfizer.ca

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