HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PREMPRO/PREMPHASE safely and effectively. See full prescribing information for PREMPRO/PREMPHASE.

PREMPRO® (conjugated estrogens/medroxyprogesterone acetate tablets) PREMPHASE® (conjugated estrogens plus medroxyprogesterone acetate tablets)
Initial U.S. Approval: 1995

WARNING: CARDIOVASCULAR DISORDERS, BREAST CANCER, ENDOMETRIAL CANCER and PROBABLE DEMENTIA
See full prescribing information for complete boxed warning.

Estrogen Plus Progestin Therapy

- **Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia (5.1, 5.3)**
- **The Women's Health Initiative (WHI) estrogen plus progestin substudy reported increased risks of stroke, deep vein thrombosis (DVT), pulmonary embolism (PE), and myocardial infarction (MI) (5.1)**
- **The WHI estrogen plus progestin substudy reported increased risks of invasive breast cancer (5.2)**
- **The WHI Memory Study (WHIMS) estrogen plus progestin ancillary study of WHI reported an increased risk of probable dementia in postmenopausal women 65 years of age and older (5.3)**

Estrogen-Alone Therapy

- **There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens (5.2)**
- **Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia (5.1, 5.3)**
- **The WHI estrogen-alone substudy reported increased risks of stroke and DVT (5.1)**
- **The WHIMS estrogen-alone ancillary study of WHI reported an increased risk of probable dementia in postmenopausal women 65 years of age and older (5.3)**

INDICATIONS AND USAGE

PREMPRO/PREMPHASE is an estrogen plus progestin indicated in a woman with a uterus for:

- Treatment of Moderate to Severe Vasomotor Symptoms due to Menopause (1.1)
- Treatment of Moderate to Severe Vulvar and Vaginal Atrophy due to Menopause (1.2)
- Prevention of Postmenopausal Osteoporosis (1.3)

DOSAGE AND ADMINISTRATION

PREMPRO: one tablet containing conjugated estrogens (CE) plus medroxyprogesterone acetate (MPA) taken orally once daily. (2)

PREMPHASE: one maroon tablet containing 0.625 mg CE taken orally on days 1 through 14, and one light-blue tablet containing 0.625 mg CE plus 5.0 mg MPA taken orally on days 15 through 28. (2)

DOSAGE FORMS AND STRENGTHS

PREMPRO Tablets: 0.3 mg CE plus 1.5 mg MPA, 0.45 mg CE plus 1.5 mg MPA, 0.625 mg CE plus 2.5 mg MPA, 0.625 mg CE plus 5 mg MPA.

PREMPHASE Tablets: 0.625 mg CE, 0.625 mg CE plus 5 mg MPA.

CONTRAINDICATIONS

- Undiagnosed abnormal genital bleeding (4)
- Known, suspected, or history of breast cancer (4, 5.2)
- Known or suspected estrogen-dependent neoplasia (4, 5.2)
- Active DVT, PE, or a history of these conditions (4, 5.1)
- Active arterial thromboembolic disease (for example, stroke and MI), or a history of these conditions (4, 5.1)
- Known anaphylactic reaction or angioedema to PREMPRO/PREMPHASE (5.15, 5.16)
- Known liver dysfunction or disease (4, 5.10)
- Known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders (4)
- Known or suspected pregnancy (4, 8.1)

WARNINGS AND PRECAUTIONS

- Estrogens increase the risk of gallbladder disease (5.4)
- Discontinue estrogen if severe hypercalcemia, loss of vision, severe hypertriglyceridemia or cholestatic jaundice occurs (5.5, 5.6, 5.9, 5.10)
- Monitor thyroid function in women on thyroid replacement therapy (5.11, 5.19)

ADVERSE REACTIONS

In two prospective, randomized clinical studies, the most common adverse reactions > 5 percent are abdominal pain, asthenia, back pain, headache, flatulence, nausea, depression, pruritus, breast pain, dysmenorrhea, and leukorrhea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer Inc. at 1-800-438-1985 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

- Inducers and/or inhibitors of CYP3A4 may affect estrogen drug metabolism (7.1)
- Aminoglutethimide administered concomitantly with MPA may significantly depress the bioavailability of medroxyprogesterone acetate (7.1)

USE IN SPECIFIC POPULATIONS

- Nursing Mothers: Estrogen administration to nursing women has been shown to decrease the quantity and quality of breast milk (8.3)
- Geriatric Use: An increased risk of probable dementia in women over 65 years of age was reported in the Women's Health Initiative Memory ancillary studies of the Women's Health Initiative (5.3, 8.5)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

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FDA-Approved Patient Labeling

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FULL PRESCRIBING INFORMATION

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Estrogen Plus Progestin Therapy

Cardiovascular Disorders and Probable Dementia

Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia *[see Warnings and Precautions (5.1, 5.3), and Clinical Studies (14.6, 14.7)]*.

The Women's Health Initiative (WHI) estrogen plus progestin substudy reported an increased risk of deep vein thrombosis (DVT), pulmonary embolism (PE), stroke and myocardial infarction (MI) in postmenopausal women (50 to 79 years of age) during 5.6 years of treatment with daily oral conjugated estrogen (CE) [0.625 mg] combined with medroxyprogesterone acetate (MPA) [2.5 mg], relative to placebo *[see Warnings and Precautions (5.1), and Clinical Studies (14.6)]*.

The WHI Memory Study (WHIMS) estrogen plus progestin ancillary study of the WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with daily CE (0.625 mg) combined with MPA (2.5 mg), relative to placebo. It is unknown whether this finding applies to younger postmenopausal women *[see Warnings and Precautions (5.3), Use in Specific Populations (8.5), and Clinical Studies (14.7)]*.

Breast Cancer

The WHI estrogen plus progestin substudy also demonstrated an increased risk of invasive breast cancer *[see Warnings and Precautions (5.2), and Clinical Studies (14.6)]*.

In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and MPA and other combinations and dosage forms of estrogens and progestins.

Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

Estrogen-Alone Therapy

Endometrial Cancer

There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. Adequate diagnostic measures, including directed or random endometrial sampling when

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indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding *[see Warnings and Precautions (5.2)]*.

Cardiovascular Disorders and Probable Dementia

Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia *[see Warnings and Precautions (5.1, 5.3), and Clinical Studies (14.6, 14.7)]*.

The WHI estrogen-alone substudy reported increased risks of stroke and DVT in postmenopausal women (50 to 79 years of age) during 7.1 years of treatment with daily oral CE (0.625 mg)-alone, relative to placebo *[see Warnings and Precautions (5.1), and Clinical Studies (14.6)]*.

The WHIMS estrogen-alone ancillary study of WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 5.2 years of treatment with daily CE (0.625 mg)-alone, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women *[see Warnings and Precautions (5.3), Use in Specific Populations (8.5), and Clinical Studies (14.7)]*.

In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and other dosage forms of estrogens.

Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

1 INDICATIONS AND USAGE

1.1 Treatment of Moderate to Severe Vasomotor Symptoms due to Menopause

1.2 Treatment of Moderate to Severe Vulvar and Vaginal Atrophy due to Menopause

1.3 Prevention of Postmenopausal Osteoporosis

2 DOSAGE AND ADMINISTRATION

Use of estrogen-alone, or in combination with a progestin, should be with the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual woman. Postmenopausal women should be re-evaluated periodically as clinically appropriate to determine if treatment is still necessary.

2.1 Treatment of Moderate to Severe Vasomotor Symptoms due to Menopause

PREMPRO therapy consists of a single tablet to be taken orally once daily.

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PREMPHASE therapy consists of two separate tablets: one maroon 0.625 mg Premarin [conjugated estrogens (CE)] tablet taken daily on days 1 through 14 and one light-blue tablet containing 0.625 mg CE and 5 mg of medroxyprogesterone acetate (MPA) taken on days 15 through 28.

2.2 Treatment of Moderate to Severe Vulvar and Vaginal Atrophy due to Menopause

PREMPRO therapy consists of a single tablet to be taken orally once daily.

PREMPHASE therapy consists of two separate tablets: one maroon 0.625 mg CE tablet taken daily on days 1 through 14 and one light-blue tablet containing 0.625 mg CE and 5 mg MPA taken on days 15 through 28.

When prescribing solely for the treatment of moderate to severe vulvar and vaginal atrophy, topical vaginal products should be considered.

2.3 Prevention of Postmenopausal Osteoporosis

PREMPRO therapy consists of a single tablet to be taken orally once daily.

PREMPHASE therapy consists of two separate tablets: one maroon 0.625 mg CE tablet taken daily on days 1 through 14 and one light-blue tablet containing 0.625 mg CE and 5 mg of MPA taken on days 15 through 28.

When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and non-estrogen medications should be carefully considered.

3 DOSAGE FORMS AND STRENGTHS

PREMPRO (conjugated estrogens/medroxyprogesterone acetate tablets)		
Tablet Strength	Tablet Shape/Color	Imprint
0.3 mg CE plus 1.5 mg MPA	oval / cream	PREMPRO 0.3/1.5
0.45 mg CE plus 1.5 mg MPA	oval / gold	PREMPRO 0.45/1.5
0.625 mg CE plus 2.5 mg MPA	oval / peach	PREMPRO 0.625/2.5
0.625 mg CE plus 5 mg MPA	oval / light blue	PREMPRO 0.625/5

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PREMPHASE (conjugated estrogens/medroxyprogesterone acetate tablets)		
Tablet Strength	Tablet Shape/Color	Imprint
0.625 mg CE	oval / maroon (14 tablets)	PREMARIN 0.625
0.625 mg CE plus 5 mg MPA	oval / light-blue (14 tablets)	PREMPRO 0.625/5

4 CONTRAINDICATIONS

PREMPRO or PREMPHASE therapy should not be used in women with any of the following conditions:

- **Undiagnosed abnormal genital bleeding**
- **Known, suspected, or history of breast cancer**
- **Known or suspected estrogen-dependent neoplasia**
- **Active DVT, PE, or a history of these conditions**
- **Active arterial thromboembolic disease (for example, stroke and MI), or a history of these conditions**
- **Known anaphylactic reaction or angioedema to PREMPRO/PREMPHASE**
- **Known liver dysfunction or disease**
- **Known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders**
- **Known or suspected pregnancy**

5 WARNINGS AND PRECAUTIONS

5.1 Cardiovascular Disorders

An increased risk of PE, DVT, stroke and MI has been reported with estrogen plus progestin therapy. An increased risk of stroke and DVT has been reported with estrogen-alone therapy. Should any of these occur or be suspected, estrogen with or without progestin therapy should be discontinued immediately.

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

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Stroke

In the WHI estrogen plus progestin substudy, a statistically significant increased risk of stroke was reported in women 50 to 79 years of age receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women in the same age group receiving placebo (33 versus 25 per 10,000 women-years) *[see Clinical Studies (14.6)]*. The increase in risk was demonstrated after the first year and persisted.[1] Should a stroke occur or be suspected, estrogen plus progestin therapy should be discontinued immediately.

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)-alone 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 1 and persisted *[see Clinical Studies (14.6)]*. Should a stroke occur or be suspected, estrogen-alone therapy should be discontinued immediately.

Subgroup analyses of women 50 to 59 years of age suggest no increased risk of stroke for those women receiving CE (0.625 mg)-alone versus those receiving placebo (18 versus 21 per 10,000 women-years).[1]

Coronary Heart Disease

In the WHI estrogen plus progestin substudy, there was a statistically non-significant increased risk of coronary heart disease (CHD) events (defined as nonfatal MI, silent MI, or CHD death) reported in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women receiving placebo (41 versus 34 per 10,000 women-years).[1] An increase in relative risk was demonstrated in year 1, and a trend toward decreasing relative risk was reported in years 2 through 5 *[see Clinical Studies (14.6)]*.

In the WHI estrogen-alone substudy, no overall effect on CHD events was reported in women receiving estrogen-alone compared to placebo[2] *[see Clinical Studies (14.6)]*.

Subgroup analyses of women 50 to 59 years of age suggest a statistically non-significant reduction in CHD events (CE [0.625 mg]-alone compared to placebo) in women with less than 10 years since menopause (8 versus 16 per 10,000 women-years).[1]

In postmenopausal women with documented heart disease (n = 2,763), average 66.7 years of age, in a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/Progestin Replacement Study [HERS]), treatment with daily CE (0.625 mg) plus MPA (2.5 mg) demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with CE 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 CE plus MPA-treated group than in the placebo group in year 1, but not during subsequent years. Two thousand, three hundred and twenty-one (2,321) women from the original HERS trial agreed to participate in an open label extension of HERS, HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. Rates of CHD events were comparable among women in the CE plus MPA group and the placebo group in HERS, HERS II, and overall.

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Venous Thromboembolism

In the WHI estrogen plus progestin substudy, a statistically significant 2-fold greater rate of VTE (DVT and PE) was reported in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women receiving placebo (35 versus 17 per 10,000 women-years). Statistically significant increases in risk for both DVT (26 versus 13 per 10,000 women-years) and PE (18 versus 8 per 10,000 women-years) were also demonstrated. The increase in VTE risk was demonstrated during the first year and persisted[3] *[see Clinical Studies (14.6)]*. Should a VTE occur or be suspected, estrogen plus progestin therapy should be discontinued immediately.

In the WHI estrogen-alone substudy, the risk of VTE was increased for women receiving daily CE (0.625 mg)-alone compared to placebo (30 versus 22 per 10,000 women-years), although only the increased risk of DVT reached statistical significance (23 versus 15 per 10,000 women-years). The increase in VTE risk was demonstrated during the first 2 years[4] *[see Clinical Studies (14.6)]*. Should a VTE occur or be suspected, estrogen-alone therapy should be discontinued immediately.

If feasible, estrogens should be discontinued at least 4 to 6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

5.2 Malignant Neoplasms

Breast Cancer

The most important randomized clinical trial providing information about breast cancer in estrogen plus progestin users is the WHI substudy of daily CE (0.625 mg) plus MPA (2.5 mg). After a mean follow-up of 5.6 years, the estrogen plus progestin substudy reported an increased risk of invasive breast cancer in women who took daily CE plus MPA. In this substudy, prior use of estrogen-alone or estrogen plus progestin therapy was reported by 26 percent of the women. The relative risk of invasive breast cancer was 1.24, and the absolute risk was 41 versus 33 cases per 10,000 women-years, for CE plus MPA compared with placebo. Among women who reported prior use of hormone therapy, the relative risk of invasive breast cancer was 1.86, and the absolute risk was 46 versus 25 cases per 10,000 women-years, for CE plus MPA compared with placebo. Among women who reported no prior use of hormone therapy, the relative risk of invasive breast cancer was 1.09, and the absolute risk was 40 versus 36 cases per 10,000 women-years, for CE plus MPA compared with placebo. In the same substudy, invasive breast cancers were larger, were more likely to be node positive, and were diagnosed at a more advanced stage in the CE (0.625 mg) plus MPA (2.5 mg) group compared with the placebo group. Metastatic disease was rare, with no apparent difference between the two groups. Other prognostic factors, such as histologic subtype, grade and hormone receptor status did not differ between the groups[5] *[see Clinical Studies (14.6)]*.

The most important randomized clinical trial providing information about breast cancer in estrogen-alone users is the WHI substudy of daily CE (0.625 mg)-alone. In the WHI estrogen-alone substudy, after an average follow-up of 7.1 years, daily CE (0.625 mg)-alone was not

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associated with an increased risk of invasive breast cancer *[relative risk (RR) 0.80]*[6] *[see Clinical Studies (14.6)]*.

Consistent with the WHI clinical trials, observational studies have also reported an increased risk of breast cancer for estrogen plus progestin therapy, and a smaller increased risk for estrogen-alone therapy, after several years of use. The risk increased with duration of use, and appeared to return to baseline over about 5 years after stopping treatment (only the observational studies have substantial data on risk after stopping). Observational studies also suggest that the risk of breast cancer was greater, and became apparent earlier, with estrogen plus progestin therapy as compared to estrogen-alone therapy. However, these studies have not found significant variation in the risk of breast cancer among different estrogen plus progestin combinations, doses, or routes of administration.

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

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

Endometrial Cancer

Endometrial hyperplasia (a possible precursor of endometrial cancer) has been reported to occur at a rate of approximately 1 percent or less with PREMPRO or PREMPHASE.

An increased risk of endometrial cancer has been reported with the use of unopposed estrogen therapy in a woman with a uterus. The reported endometrial cancer risk among unopposed estrogen users is about 2 to 12 times greater than in non-users, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with use of estrogens for less than 1 year. The greatest risk appears to be associated with prolonged use, with increased risks of 15- to 24-fold for 5 to 10 years or more, and this risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued.

Clinical surveillance of all women using estrogen-alone or estrogen plus progestin therapy is important. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding.

There is no evidence that the use of natural estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent estrogen dose. Adding a progestin to estrogen therapy in postmenopausal women has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.

Ovarian Cancer

The WHI estrogen plus progestin substudy reported a statistically non-significant increased risk of ovarian cancer. After an average follow-up of 5.6 years, the relative risk for ovarian cancer for CE plus MPA versus placebo was 1.58 (95 percent CI, 0.77-3.24). The absolute risk for CE plus

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MPA versus placebo was 4 versus 3 cases per 10,000 women-years.[7] In some epidemiologic studies, the use of estrogen plus progestin and estrogen-only products, in particular for 5 or more years, has been associated with an increased risk of ovarian cancer. However, the duration of exposure associated with increased risk is not consistent across all epidemiologic studies, and some report no association.

5.3 Probable Dementia

In the WHIMS estrogen plus progestin ancillary study of WHI, a population of 4,532 postmenopausal women 65 to 79 years of age was randomized to daily CE (0.625 mg) plus MPA (2.5 mg) or placebo.

After an average follow-up of 4 years, 40 women in the CE plus MPA group and 21 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE plus MPA versus placebo was 2.05 (95 percent CI, 1.21-3.48). The absolute risk of probable dementia for CE plus MPA versus placebo was 45 versus 22 cases per 10,000 women-years[8] *[see Use in Specific Populations (8.5), and Clinical Studies (14.7)]*.

In the WHIMS estrogen-alone ancillary study of WHI, a population of 2,947 hysterectomized women 65 to 79 years of age was randomized to daily CE (0.625 mg)-alone or placebo.

After an average follow-up of 5.2 years, 28 women in the estrogen-alone group and 19 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE-alone versus placebo was 1.49 (95 percent CI, 0.83-2.66). The absolute risk of probable dementia for CE-alone versus placebo was 37 versus 25 cases per 10,000 women-years[8] *[see Use in Specific Populations (8.5), and Clinical Studies (14.7)]*.

When data from the two populations in the WHIMS estrogen-alone and estrogen plus progestin ancillary studies were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.76 (95 percent CI, 1.19-2.60). 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[8] *[see Use in Specific Populations (8.5), and Clinical Studies (14.7)]*.

5.4 Gallbladder Disease

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

5.5 Hypercalcemia

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

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5.6 Visual Abnormalities

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

5.7 Addition of a Progestin When a Woman Has Not Had a Hysterectomy

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

There are, however, possible risks that may be associated with the use of progestins with estrogens compared to estrogen-alone regimens. These include an increased risk of breast cancer.

5.8 Elevated Blood Pressure

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

5.9 Hypertriglyceridemia

In women with pre-existing hypertriglyceridemia, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis. Consider discontinuation of treatment if pancreatitis occurs.

5.10 Hepatic Impairment and/or Past History of Cholestatic Jaundice

Estrogens may be poorly metabolized in women with impaired liver function. For women with a history of cholestatic jaundice associated with past estrogen use or with pregnancy, caution should be exercised, and in the case of recurrence, medication should be discontinued.

5.11 Hypothyroidism

Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Women with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T_4 and T_3 serum concentrations in the normal range. 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.

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5.12 Fluid Retention

Estrogens plus progestins may cause some degree of fluid retention. Women with conditions that might be influenced by this factor, such as cardiac or renal dysfunction, warrant careful observation when estrogens plus progestins are prescribed.

5.13 Hypocalcemia

Estrogen therapy should be used with caution in women with hypoparathyroidism as estrogen-induced hypocalcemia may occur.

5.14 Exacerbation of Endometriosis

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

5.15 Anaphylactic Reaction and Angioedema

Cases of anaphylaxis, which developed within minutes to hours after taking PREMPRO or PREMPHASE and require emergency medical management, have been reported in the postmarketing setting. Skin (hives, pruritis, swollen lips-tongue-face) and either respiratory tract (respiratory compromise) or gastrointestinal tract (abdominal pain, vomiting) involvement has been noted.

Angioedema involving the tongue, larynx, face, hands, and feet requiring medical intervention has occurred postmarketing in patients taking PREMPRO or PREMPHASE. If angioedema involves the tongue, glottis, or larynx, airway obstruction may occur. Patients who develop an anaphylactic reaction with or without angioedema after treatment with PREMPRO or PREMPHASE should not receive PREMPRO or PREMPHASE again.

5.16 Hereditary Angioedema

Exogenous estrogens may exacerbate symptoms of angioedema in women with hereditary angioedema.

5.17 Exacerbation of Other Conditions

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

5.18 Laboratory Tests

Serum follicle stimulating hormone (FSH) and estradiol levels have not been shown to be useful in the management of moderate to severe vasomotor symptoms and moderate to severe symptoms of vulvar and vaginal atrophy.

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5.19 Drug-Laboratory Test Interactions

Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex, and beta-thromboglobulin; decreased levels of antifactor Xa and antithrombin III, decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.

Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T_4 levels (by column or by radioimmunoassay), or T_3 levels by radioimmunoassay. T_3 resin uptake is decreased, reflecting the elevated TBG. Free T_4 and free T_3 concentrations are unaltered. Women on thyroid replacement therapy may require higher doses of thyroid hormone.

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

Increased plasma high-density lipoprotein (HDL) and HDL_2 cholesterol subfraction concentrations, reduced low-density lipoprotein (LDL) cholesterol concentrations, increased triglyceride levels.

Impaired glucose tolerance.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Cardiovascular Disorders *[see Boxed Warning, Warnings and Precautions (5.1)]*
- Malignant Neoplasms *[see Boxed Warning, Warnings and Precautions (5.2)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trial of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In a 1-year clinical trial that included 678 postmenopausal women treated with PREMPRO and 351 postmenopausal women treated with PREMPHASE, the following adverse reactions occurred at a rate ≥ 1 percent, see Table 1.

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TABLE 1: ALL TREATMENT RELATED ADVERSE REACTIONS AT A FREQUENCY ≥ 1 PERCENT

Body System Adverse event	PREMPRO 0.625 mg/2.5 mg continuous (n = 340)	PREMPRO 0.625 mg/5 mg continuous (n = 338)	PREMPHASE 0.625 mg/5 mg sequential (n = 351)
Body As A Whole			
Abdominal pain	35 (10%)	51 (15%)	58 (17%)
Asthenia	13 (4%)	18 (5%)	21 (6%)
Back pain	19 (6%)	16 (5%)	23 (7%)
Chest pain	5 (1%)	4 (1%)	4 (1%)
Flu syndrome	1 (<1%)	1 (<1%)	4 (1%)
Generalized edema	12 (4%)	12 (4%)	8 (2%)
Headache	64 (19%)	52 (15%)	66 (19%)
Infection	2 (<1%)	4 (1)%	0
Moniliasis	4 (1%)	3 (<1%)	4 (1%)
Pain	12 (4%)	14 (4%)	15 (4%)
Pelvic pain	11 (3%)	13 (4%)	16 (5%)
Cardiovascular System			
Hypertension	7 (2%)	7 (2%)	6 (2%)
Migraine	6 (2%)	8 (2%)	7 (2%)
Palpitation	2 (<1%)	3 (<1%)	4 (1%)
Vasodilatation	2 (<1%)	7 (2%)	2 (<1%)
Digestive System			
Diarrhea	4 (1%)	3 (<1%)	7 (2%)
Dyspepsia	5 (1%)	5 (1%)	7 (2%)
Eructation	0	2 (<1%)	4 (1%)
Flatulence	25 (7%)	27 (8%)	24 (7%)
Increased appetite	1 (<1%)	5 (1%)	5 (1%)
Nausea	26 (8%)	19 (6%)	26 (7%)
Metabolic and Nutritional			
Edema	5 (1%)	6 (2%)	3 (<1%)
Glucose tolerance decreased	2 (<1%)	5 (1%)	4 (1%)
Peripheral edema	11 (3%)	10 (3%)	11 (3%)
Weight gain	9 (3%)	10 (3%)	11 (3%)
Musculoskeletal System			
Arthralgia	6 (2%)	2 (<1%)	7 (2%)
Leg cramps	8 (2%)	11 (3%)	12 (3%)
Nervous System			

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TABLE 1: ALL TREATMENT RELATED ADVERSE REACTIONS AT A FREQUENCY ≥ 1 PERCENT

Body System Adverse event	PREMPRO 0.625 mg/2.5 mg continuous (n = 340)	PREMPRO 0.625 mg/5 mg continuous (n = 338)	PREMPHASE 0.625 mg/5 mg sequential (n = 351)
Depression	14 (4%)	26 (8%)	29 (8%)
Dizziness	9 (3%)	8 (2%)	7 (2%)
Emotional lability	5 (1%)	5 (1%)	6 (2%)
Hypertonia	4 (1%)	4 (1%)	7 (2%)
Insomnia	7 (2%)	6 (2%)	4 (1%)
Nervousness	4 (1%)	9 (3%)	6 (2%)
Skin and Appendages			
Acne	1 (<1%)	5 (1%)	4 (1%)
Alopecia	3 (<1%)	4 (1%)	0
Dry skin	2 (<1%)	3 (<1%)	4 (1%)
Pruritus	20 (6%)	18 (5%)	13 (4%)
Rash	8 (2%)	6 (2%)	7 (2%)
Sweating	2 (<1%)	4 (1%)	2 (<1%)
Urogenital System			
Breast engorgement	5 (1%)	5 (1%)	0
Breast enlargement	14 (4%)	14 (4%)	14 (4%)
Breast neoplasm	2 (<1%)	2 (<1%)	4 (1%)
Breast pain	110 (32%)	123 (36%)	109 (31%)
Cervix disorder	10 (3%)	6 (2%)	10 (3%)
Dysmenorrhea	26 (8%)	18 (5%)	44 (13%)
Leukorrhea	19 (6%)	13 (4%)	29 (8%)
Menstrual disorder	7 (2%)	1 (<1%)	5 (1%)
Menorrhagia	0	1 (<1%)	5 (1%)
Metrorrhagia	13 (4%)	5 (1%)	7 (1%)
Papanicolaou smear suspicious	5 (1%)	0	8 (2%)
Urinary incontinence	4 (1%)	2 (<1%)	1 (<1%)
Uterine spasm	7 (2%)	4 (1%)	7 (2%)
Vaginal hemorrhage	5 (1%)	3 (<1%)	8 (2%)
Vaginal moniliasis	5 (1%)	6 (2%)	7 (2%)
Vaginitis	13 (4%)	13 (4%)	10 (3%)

In addition, phargyngitis and sinusitis were reported as two of the more frequent adverse events (>5 percent) in the PREMPRO clinical study. For pharyngitis, of the 121 events, six events were

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considered by the investigator causally related to study drug. For sinusitis, of the 73 events, one event was considered as casually related to study drug.

During the first year of a 2-year clinical trial with postmenopausal women between 40 and 65 years of age (88 percent Caucasian), 989 postmenopausal women received continuous regimens of PREMPRO, and 332 received placebo tablets. Table 2 summarizes adverse reactions that occurred at a rate ≥ 1 percent in at least 1 treatment group.

TABLE 2: ALL TREATMENT RELATED ADVERSE REACTIONS AT A FREQUENCY OF ≥ 1 PERCENT

Body System Adverse event	PREMPRO 0.625/2.5 continuous (N=331)	PREMPRO 0.45/1.5 continuous (N=331)	PREMPRO 0.3/1.5 continuous (N=327)	PLACEBO daily (N=332)
Any adverse event	214 (65)	208 (63)	188 (57)	164 (49)
Body as a Whole				
Abdominal pain	38 (11)	33 (10)	24 (7)	21 (6)
Asthenia	11 (3)	11 (3)	12 (4)	3 (1)
Back pain	12 (4)	12 (4)	8 (2)	4 (1)
Chest pain	4 (1)	2 (1)	1 (0)	2 (1)
Generalized edema	7 (2)	5 (2)	6 (2)	8 (2)
Headache	45 (14)	45 (14)	57 (17)	46 (14)
Moniliasis	3 (1)	6 (2)	4 (1)	1 (0)
Pain	9 (3)	10 (3)	17 (5)	14 (4)
Pelvic pain	9 (3)	7 (2)	5 (2)	4 (1)
Cardiovascular System				
Hypertension	2 (1)	3 (1)	1 (0)	5 (2)
Migraine	11 (3)	8 (2)	5 (2)	3 (1)
Palpitation	1 (0)	1 (0)	2 (1)	4 (1)
Vasodilatation	0	3 (1)	1 (0)	5 (2)
Digestive System				
Constipation	5 (2)	7 (2)	6 (2)	3 (1)
Diarrhea	5 (2)	2 (1)	6 (2)	8 (2)
Dyspepsia	10 (3)	9 (3)	6 (2)	14 (4)
Flatulence	16 (5)	18 (5)	13 (4)	8 (2)
Increased appetite	6 (2)	2 (1)	0	2 (1)
Nausea	13 (4)	13 (4)	16 (5)	16 (5)
Metabolic and nutritional				
Peripheral edema	7 (2)	8 (2)	4 (1)	3 (1)
Weight gain	9 (3)	8 (2)	6 (2)	14 (4)
Musculoskeletal System				
Arthralgia	2 (1)	3 (1)	3 (1)	5 (2)
Leg cramps	13 (4)	7 (2)	10 (3)	4 (1)
Nervous System				
Anxiety	5 (2)	4 (1)	1 (0)	4 (1)

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TABLE 2: ALL TREATMENT RELATED ADVERSE REACTIONS AT A FREQUENCY OF ≥ 1 PERCENT

Body System Adverse event	PREMPRO 0.625/2.5 continuous (N=331)	PREMPRO 0.45/1.5 continuous (N=331)	PREMPRO 0.3/1.5 continuous (N=327)	PLACEBO daily (N=332)
Depression	23 (7)	11 (3)	11 (3)	17 (5)
Dizziness	3 (1)	8 (2)	6 (2)	5 (2)
Emotional lability	10 (3)	10 (3)	9 (3)	8 (2)
Insomnia	8 (2)	7 (2)	9 (3)	14 (4)
Nervousness	6 (2)	3 (1)	4 (1)	6 (2)
Skin and Appendages				
Acne	7 (2)	3 (1)	0	3 (1)
Alopecia	1 (0)	6 (2)	4 (1)	2 (1)
Pruritus	8 (2)	10 (3)	9 (3)	3 (1)
Rash	0	6 (2)	4 (1)	2 (1)
Skin discoloration	5 (2)	1 (0)	3 (1)	1 (0)
Sweating	3 (1)	1 (0)	0	4 (1)
Urogenital System				
Breast disorder	7 (2)	6 (2)	5 (2)	6 (2)
Breast enlargement	18 (5)	9 (3)	5 (2)	3 (1)
Breast neoplasm	8 (2)	7 (2)	5 (2)	7 (2)
Breast pain	87 (26)	66 (20)	41 (13)	26 (8)
Cervix disorder	7 (2)	2 (1)	2 (1)	0
Dysmenorrhea	14 (4)	18 (5)	9 (3)	2 (1)
Hematuria	4 (1)	3 (1)	1 (0)	2 (1)
Leukorrhea	7 (2)	14 (4)	9 (3)	6 (2)
Metrorrhagia	7 (2)	14 (4)	4 (1)	1 (0)
Urinary tract infection	0	1 (0)	1 (0)	4 (1)
Uterine spasm	13 (4)	11 (3)	7 (2)	2 (1)
Vaginal dryness	2 (1)	1 (0)	0	6 (2)
Vaginal hemorrhage	18 (5)	14 (4)	7 (2)	0
Vaginal moniliasis	13 (4)	11 (3)	8 (2)	5 (2)
Vaginitis	6 (2)	8 (2)	7 (2)	1 (0)

In addition, the following events were considered as related to the study drug with an incidence less than 1 percent, including accidental injury, infection, myalgia, cough increased, rhinitis, sinusitis, and upper respiratory infection.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of PREMPRO or PREMPHASE. Because these reactions are reported voluntarily from a population of uncertain

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size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Genitourinary System

Abnormal uterine bleeding, dysmenorrhea or pelvic pain, increase in size of uterine leiomyomata, vaginitis, vaginal candidiasis, amenorrhea, changes in cervical secretion, ovarian cancer, endometrial hyperplasia, endometrial cancer.

Breasts

Tenderness, enlargement, pain, nipple discharge, galactorrhea, fibrocystic breast changes, breast cancer.

Cardiovascular

Deep and superficial venous thrombosis, pulmonary embolism, superficial thrombophlebitis, myocardial infarction, stroke, increase in blood pressure.

Gastrointestinal

Nausea, vomiting, abdominal pain, bloating, cholestatic jaundice, increased incidence of gallbladder disease, pancreatitis, changes in appetite, ischemic colitis.

Skin

Chloasma or melasma that may persist when drug is discontinued, erythema multiforme, erythema nodosum, loss of scalp hair, hirsutism, pruritus, urticaria, rash, acne.

Eyes

Retinal vascular thrombosis, intolerance of contact lenses.

Central Nervous System

Headache, migraine, dizziness, mental depression, exacerbation of chorea, mood disturbances, anxiety, irritability, exacerbation of epilepsy, dementia, growth potentiation of benign meningioma.

Miscellaneous

Increase or decrease in weight, arthralgia, glucose intolerance, edema, changes in libido, exacerbation of asthma, increased triglycerides, hypersensitivity.

Additional postmarketing adverse reactions have been reported in patients receiving other forms of hormone therapy.

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7 DRUG INTERACTIONS

Data from a single-dose drug-drug interaction study involving conjugated estrogens and medroxyprogesterone acetate indicate that the pharmacokinetic disposition of both drugs is not altered when the drugs are coadministered. No other clinical drug-drug interaction studies have been conducted with CE plus MPA.

7.1 Metabolic Interactions

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, carbamazepine, and rifampin, may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4, such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice, may increase plasma concentrations of estrogens and may result in side effects.

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

PREMPRO and PREMPHASE should not be used during pregnancy *[see Contraindications (4)]*. There appears to be little or no increased risk of birth defects in children born to women who have used estrogens and progestins as an oral contraceptive inadvertently during early pregnancy.

8.3 Nursing Mothers

PREMPRO and PREMPHASE should not be used during lactation. Estrogen administration to nursing women has been shown to decrease the quantity and quality of the breast milk. Detectable amounts of estrogen and progestin have been identified in the breast milk of women receiving these drugs. Caution should be exercised when PREMPRO or PREMPHASE is administered to a nursing woman.

8.4 Pediatric Use

PREMPRO and PREMPHASE are not indicated in children. Clinical studies have not been conducted in the pediatric population.

8.5 Geriatric Use

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

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The Women's Health Initiative Studies

In the WHI estrogen plus progestin substudy (daily CE [0.625 mg] plus MPA [2.5 mg] versus placebo), there was a higher relative risk of nonfatal stroke and invasive breast cancer in women greater than 65 years of age *[see Clinical Studies (14.6)]*.

In the WHI estrogen-alone substudy (daily CE [0.625 mg]-alone versus placebo), there was a higher relative risk of stroke in women greater than 65 years of age *[see Clinical Studies (14.6)]*.

The Women's Health Initiative Memory Study

In the WHIMS ancillary studies 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 *[see Warnings and Precautions (5.3), and Clinical Studies (14.7)]*.

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[8] *[see Warnings and Precautions (5.3), and Clinical Studies (14.7)]*.

8.6 Renal Impairment

The effects of renal impairment on the pharmacokinetics of PREMPRO or PREMPHASE have not been studied.

8.7 Hepatic Impairment

The effects of hepatic impairment on the pharmacokinetics of PREMPRO or PREMPHASE have not been studied.

10 OVERDOSAGE

Overdosage of estrogen plus progestin may cause nausea, vomiting, breast tenderness, abdominal pain, drowsiness and fatigue, and withdrawal bleeding may occur in women. Treatment of overdose consists of discontinuation of PREMPRO or PREMPHASE therapy with institution of appropriate symptomatic care.

11 DESCRIPTION

Premarin (conjugated estrogens tablets, USP) for oral administration contains a mixture 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 sodium estrone sulfate and sodium equilin sulfate. It contains as concomitant components, as sodium sulfate conjugates, 17 α-dihydroequilin, 17 α-estradiol and 17 β-dihydroequilin.

Medroxyprogesterone acetate is a derivative of progesterone. It is a white to off-white, odorless, crystalline powder, stable in air, melting between 200°C and 210°C. It is freely soluble in

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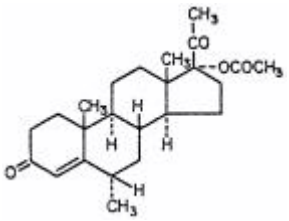
chloroform, soluble in acetone and in dioxane, sparingly soluble in alcohol and in methanol, slightly soluble in ether, and insoluble in water. The chemical name for MPA is pregn-4-ene-3, 20-dione, 17-(acetyloxy)-6-methyl-, (6α)-. Its molecular formula is $C_{24}H_{34}O_4$, with a molecular weight of 386.53. Its structural formula is:



PREMPRO 0.3 mg/1.5 mg and 0.45 mg/1.5 mg tablets contain the following inactive ingredients: calcium phosphate tribasic, microcrystalline cellulose, carnauba wax, hypromellose, hydroxypropyl cellulose, sucrose, Eudragit NE 30D, lactose monohydrate, magnesium stearate, polyethylene glycol, titanium dioxide, yellow iron oxide, propylene glycol and black iron oxide.

PREMPRO 0.625 mg/2.5 mg tablets contain the following inactive ingredients: calcium phosphate tribasic, microcrystalline cellulose, hypromellose, hydroxypropyl cellulose, sucrose, Eudragit NE 30D, lactose monohydrate, magnesium stearate, polyethylene glycol, povidone, titanium dioxide, red iron oxide, yellow iron oxide, and black iron oxide.

PREMPRO 0.625 mg/5 mg tablets contain the following inactive ingredients: calcium phosphate tribasic, carnauba wax, Eudragit NE 30D, hydroxypropyl cellulose, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sucrose, titanium dioxide, FD&C Blue No. 2, and black iron oxide.

PREMPHASE

Each maroon Premarin tablets for oral administration contain 0.625 mg of conjugated estrogens and the following inactive ingredients: calcium phosphate tribasic, hydroxypropyl cellulose, microcrystalline cellulose, powdered cellulose, hypromellose, lactose monohydrate, magnesium stearate, polyethylene glycol, sucrose, titanium dioxide, FD&C Blue No. 2, and FD&C Red No. 40. These tablets comply with USP Dissolution Test 5.

Each light-blue tablet for oral administration contains 0.625 mg of conjugated estrogens, 5 mg of medroxyprogesterone acetate, and the following inactive ingredients: calcium phosphate tribasic, carnauba wax, Eudragit NE 30D, hydroxypropyl cellulose, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sucrose, titanium dioxide, FD&C Blue No. 2, and black iron oxide.

PREMPRO

Tablet Strength	Tablet Color Contains

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Tablet Strength	Tablet Color Contains
0.3 mg/1.5 mg	Yellow iron oxide and black iron oxide
0.45 mg/1.5 mg	Yellow iron oxide and black iron oxide
0.625 mg/2.5 mg	Red iron oxide, yellow iron oxide, and black iron oxide
0.625 mg/5 mg	FD&C Blue No. 2 and black iron oxide

PREMPHASE

Tablet Strength	Tablet Color Contains
0.625 mg	FD&C Blue No. 2 and FD&C Red No. 40
0.625 mg/5 mg	FD&C Blue No. 2 and black iron oxide

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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, which is secreted by the adrenal cortex, to estrone in the 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 FSH, through a negative feedback mechanism. Estrogens act to reduce the elevated levels of these gonadotropins seen in postmenopausal women.

Parenterally administered medroxyprogesterone acetate (MPA) inhibits gonadotropin production, which in turn prevents follicular maturation and ovulation; although available data indicate that

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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.

12.2 Pharmacodynamics

Currently, there are no pharmacodynamic data known for PREMPRO or PREMPHASE tablets.

12.3 Pharmacokinetics

Absorption

PREMPRO and PREMPHASE contain a formulation of medroxyprogesterone acetate (MPA) that is immediately released and conjugated estrogens that are slowly released over several hours. Conjugated estrogens are water-soluble and are well-absorbed from the gastrointestinal tract after release from the drug formulation. MPA is well absorbed from the gastrointestinal tract. Table 3 and Table 4 summarize the mean pharmacokinetic parameters for select unconjugated and conjugated estrogens and medroxyprogesterone acetate following administration of PREMPRO to healthy, postmenopausal women.

TABLE 3: PHARMACOKINETIC PARAMETERS FOR UNCONJUGATED AND CONJUGATED ESTROGENS (CE) AND MEDROXYPROGESTERONE ACETATE (MPA)

DRUG	2 x 0.625 mg CE/2.5 mg MPA Combination Tablets (n = 54)				2 x 0.625 mg CE/5 mg MPA Combination Tablets (n = 51)			
PK Parameter Arithmetic Mean (%CV)	**C_{max}** (pg/mL)	**t_{max}** (h)	**$t_{1/2}$** (h)	**AUC** (pg•h/mL)	**C_{max}** (pg/mL)	**t_{max}** (h)	**$t_{1/2}$** (h)	**AUC** (pg•h/mL)
Unconjugated Estrogens								
Estrone	175 (23)	7.6 (24)	31.6 (23)	5358 (34)	124 (43)	10 (35)	62.2 (137)	6303 (40)
BA* -Estrone	159 (26)	7.6 (24)	16.9 (34)	3313 (40)	104 (49)	10 (35)	26.0 (100)	3136 (51)
Equilin	71 (31)	5.8 (34)	9.9 (35)	951 (43)	54 (43)	8.9 (34)	15.5 (53)	1179 (56)
PK Parameter Arithmetic Mean (%CV)	**C_{max}** (ng/mL)	**t_{max}** (h)	**$t_{1/2}$** (h)	**AUC** (ng•h/mL)	**C_{max}** (ng/mL)	**t_{max}** (h)	**$t_{1/2}$** (h)	**AUC** (ng•h/mL)
Conjugated Estrogens								
Total Estrone	6.6 (38)	6.1 (28)	20.7 (34)	116 (59)	6.3 (48)	9.1 (29)	23.6 (36)	151 (42)
BA* -Total Estrone	6.4 (39)	6.1 (28)	15.4 (34)	100 (57)	6.2 (48)	9.1 (29)	20.6 (35)	139 (40)

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TABLE 3: PHARMACOKINETIC PARAMETERS FOR UNCONJUGATED AND CONJUGATED ESTROGENS (CE) AND MEDROXYPROGESTERONE ACETATE (MPA)

DRUG	2 x 0.625 mg CE/2.5 mg MPA Combination Tablets (n = 54)				2 x 0.625 mg CE/5 mg MPA Combination Tablets (n = 51)			
Total Equilin	5.1 (45)	4.6 (35)	11.4 (25)	50 (70)	4.2 (52)	7.0 (36)	17.2 (131)	72 (50)
PK Parameter Arithmetic Mean (%CV)	**C_{max}** (ng/mL)	**t_{max}** (h)	**$t_{1/2}$** (h)	**AUC** (ng•h/mL)	**C_{max}** (ng/mL)	**t_{max}** (h)	**$t_{1/2}$** (h)	**AUC** (ng•h/mL)
Medroxyprogesterone Acetate								
MPA	1.5 (40)	2.8 (54)	37.6 (30)	37 (30)	4.8 (31)	2.4 (50)	46.3 (39)	102 (28)

BA* = Baseline adjusted
C_{max} = peak plasma concentration
t_{max} = time peak concentration occurs
$t_{1/2}$ = apparent terminal-phase disposition half-life ($0.693/\lambda_z$)
AUC = total area under the concentration-time curve

TABLE 4. PHARMACOKINETIC PARAMETERS FOR UNCONJUGATED AND CONJUGATED ESTROGENS (CE) AND MEDROXYPROGESTERONE ACETATE (MPA)

DRUG	4 x 0.45 mg CE/1.5 mg MPA Combination (n = 65)			
PK Parameter Arithmetic Mean (%CV)	**C_{max}** (pg/mL)	**t_{max}** (h)	**$t_{1/2}$** (h)	**AUC** (pg•h/mL)
Unconjugated Estrogens				
Estrone	149 (35)	8.9 (35)	37.5 (35)	6641 (39)
BA* -Estrone	130 (40)	8.9 (35)	21.2 (35)	3799 (47)
Equilin	83 (38)	8.3 (48)	15.9 (44)	1889 (40)

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TABLE 4. PHARMACOKINETIC PARAMETERS FOR UNCONJUGATED AND CONJUGATED ESTROGENS (CE) AND MEDROXYPROGESTERONE ACETATE (MPA)

DRUG	4 x 0.45 mg CE/1.5 mg MPA Combination (n = 65)			
PK Parameter Arithmetic Mean (%CV)	**C_{max}** (ng/mL)	**t_{max}** (h)	**$t_{1/2}$** (h)	**AUC** (ng•h/mL)
Conjugated Estrogens				
Total Estrone	5.4 (49)	7.9 (48)	22.4 (53)	119 (48)
BA* -Total Estrone	5.2 (48)	7.9 (48)	15.1 (29)	100 (47)
Total Equilin	4.3 (42)	6.5 (45)	11.6 (31)	74 (48)
PK Parameter Arithmetic Mean (%CV)	**C_{max}** (ng/mL)	**t_{max}** (h)	**$t_{1/2}$** (h)	**AUC** (ng•h/mL)
Medroxyprogesterone Acetate				
MPA	0.7 (66)	2.0 (52)	26.2 (35)	5.0 (61)

BA* = Baseline adjusted
C_{max} = peak plasma concentration
t_{max} = time peak concentration occurs
$t_{1/2}$ = apparent terminal-phase disposition half-life ($0.693/\lambda_z$)
AUC = total area under the concentration-time curve

Food-Effect: Single dose studies in healthy, postmenopausal women were conducted to investigate any potential drug interaction when PREMPRO or PREMPHASE is administered with a high-fat breakfast. Administration with food decreased the C_{max} of total estrone by 18 to 34 percent and increased total equilin C_{max} by 38 percent compared to the fasting state, with no other effect on the rate or extent of absorption of other conjugated or unconjugated estrogens. Administration with food approximately doubles MPA C_{max} and increases MPA AUC by approximately 20 to 30 percent.

Dose Proportionality: The C_{max} and AUC values for MPA observed in two separate pharmacokinetic studies conducted with 2 PREMPRO 0.625 mg/2.5 mg or 2 PREMPRO or PREMPHASE 0.625 mg/5 mg tablets exhibited nonlinear dose proportionality; doubling the MPA dose from 2 x 2.5 to 2 x 5 mg increased the mean C_{max} and AUC by 3.2- and 2.8-fold, respectively.

The dose proportionality of estrogens and medroxyprogesterone acetate was assessed by combining pharmacokinetic data across another two studies totaling 61 healthy, postmenopausal women. Single conjugated estrogens doses of 2 x 0.3 mg, 2 x 0.45 mg, or 2 x 0.625 mg were administered either alone or in combination with medroxyprogesterone acetate doses of 2 x 1.5 mg or 2 x 2.5 mg. Most of the estrogen components demonstrated dose proportionality;

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however, several estrogen components did not. Medroxyprogesterone acetate pharmacokinetic parameters increased in a dose-proportional manner.

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 SHBG and albumin. MPA is approximately 90 percent bound to plasma proteins, but does not bind to SHBG.

Metabolism

Exogenous estrogens are metabolized in the same manner as endogenous estrogens. Circulating estrogens exist in a dynamic equilibrium of metabolic interconversions. These transformations take place mainly in the liver. Estradiol is converted reversibly to estrone, and both can be converted to estriol, which is a major urinary metabolite. Estrogens also undergo enterohepatic recirculation via sulfate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestine, and hydrolysis in the intestine followed by reabsorption. In postmenopausal women, a significant portion of the circulating estrogens exists as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogens. Metabolism and elimination of MPA occur primarily in the liver via hydroxylation, with subsequent conjugation and elimination in the urine.

Excretion

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.

Use in Specific Populations

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

14 CLINICAL STUDIES

14.1 Effects on Vasomotor Symptoms

In the first year of the Health and Osteoporosis, Progestin and Estrogen (HOPE) Study, a total of 2,805 postmenopausal women (average age 53.3 ± 4.9 years) were randomly assigned to one of eight treatment groups of either placebo or conjugated estrogens, with or without

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medroxyprogesterone acetate. Efficacy for vasomotor symptoms was assessed during the first 12 weeks of treatment in a subset of symptomatic women (n = 241) who had at least seven moderate to severe hot flushes daily, or at least 50 moderate to severe hot flushes during the week before randomization. With PREMPRO 0.625 mg/2.5 mg, 0.45 mg/1.5 mg, and 0.3 mg/1.5 mg, the relief of both the frequency and severity of moderate to severe vasomotor symptoms was shown to be statistically improved compared to placebo at weeks 4 and 12. Table 5 shows the adjusted mean number of hot flushes in the PREMPRO 0.625 mg/2.5 mg, 0.45 mg/1.5 mg, 0.3 mg/1.5 mg, and placebo groups during the initial 12-week period.

TABLE 5: SUMMARY TABULATION OF THE NUMBER OF HOT FLUSHES PER DAY – MEAN VALUES AND COMPARISONS BETWEEN THE ACTIVE TREATMENT GROUPS AND THE PLACEBO GROUP – PATIENTS WITH AT LEAST 7 MODERATE TO SEVERE FLUSHES PER DAY OR AT LEAST 50 PER WEEK AT BASELINE, LAST OBSERVATION CARRIED FORWARD (LOCF)

Treatment[a] (No. of Patients)	----------No. of Hot Flushes/Day----------			
Time Period (week)	Baseline Mean ± SD	Observed Mean ± SD	Mean Change ± SD	p-Values vs. Placebo[b]
0.625 mg/2.5 mg (n = 34)				
4	11.98 ± 3.54	3.19 ± 3.74	-8.78 ± 4.72	<0.001
12	11.98 ± 3.54	1.16 ± 2.22	-10.82 ± 4.61	<0.001
0.45 mg/1.5 mg (n = 29)				
4	12.61 ± 4.29	3.64 ± 3.61	-8.98 ± 4.74	<0.001
12	12.61 ± 4.29	1.69 ± 3.36	-10.92 ± 4.63	<0.001
0.3 mg/1.5 mg (n = 33)				
4	11.30 ± 3.13	3.70 ± 3.29	-7.60 ± 4.71	<0.001
12	11.30 ± 3.13	1.31 ± 2.82	-10.00 ± 4.60	<0.001
Placebo (n = 28)				
4	11.69 ± 3.87	7.89 ± 5.28	-3.80 ± 4.71	-
12	11.69 ± 3.87	5.71 ± 5.22	-5.98 ± 4.60	-

[a] Identified by dosage (mg) of Premarin/MPA or placebo.
[b] There were no statistically significant differences between the 0.625 mg/2.5 mg, 0.45 mg/1.5 mg, and 0.3 mg/1.5 mg groups at any time period.

14.2 Effects on Vulvar and Vaginal Atrophy

Results of vaginal maturation indexes at cycles 6 and 13 showed that the differences from placebo were statistically significant ($p < 0.001$) for all treatment groups.

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14.3 Effects on the Endometrium

In a 1-year clinical trial of 1,376 women (average age 54 ± 4.6 years) randomized to PREMPRO 0.625 mg/2.5 mg (n = 340), PREMPRO 0.625 mg/5 mg (n = 338), PREMPHASE 0.625 mg/5 mg (n = 351), or Premarin 0.625 mg alone (n = 347), results of evaluable biopsies at 12 months (n = 279, 274, 277, and 283, respectively) showed a reduced risk of endometrial hyperplasia in the two PREMPRO treatment groups (less than 1 percent) and in the PREMPHASE treatment group (less than 1 percent; 1 percent when focal hyperplasia was included) compared to the Premarin group (8 percent; 20 percent when focal hyperplasia was included), see Table 6.

TABLE 6: INCIDENCE OF ENDOMETRIAL HYPERPLASIA AFTER ONE YEAR OF TREATMENT

	----------Groups----------			
	PREMPRO 0.625 mg/ 2.5 mg	PREMPRO 0.625 mg/ 5 mg	PREMPHASE 0.625 mg/ 5 mg	Premarin 0.625 mg
Total number of patients	340	338	351	347
Number of patients with evaluable biopsies	279	274	277	283
No. (%) of patients with biopsies:				
• All focal and non-focal hyperplasia	2 (<1)*	0 (0)*	3 (1)*	57 (20)
• Excluding focal cystic hyperplasia	2 (<1)*	0 (0)*	1 (<1)*	25 (8)

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

In the first year of the Health and Osteoporosis, Progestin and Estrogen (HOPE) Study, 2,001 women (average age 53.3 ± 4.9 years), of whom 88 percent were Caucasian, were treated with either Premarin 0.625 mg alone (n = 348), Premarin 0.45 mg alone (n = 338), Premarin 0.3 mg alone (n = 326) or PREMPRO 0.625 mg/2.5 mg (n = 331), PREMPRO 0.45 mg/1.5 mg (n = 331) or PREMPRO 0.3 mg/1.5 mg (n = 327). Results of evaluable endometrial biopsies at 12 months showed a reduced risk of endometrial hyperplasia or cancer in the PREMPRO treatment groups compared with the corresponding Premarin alone treatment groups, except for the PREMPRO 0.3 mg/1.5 mg and Premarin 0.3 mg alone groups, in each of which there was only 1 case, see Table 7.

No endometrial hyperplasia or cancer was noted in those patients treated with the continuous combined regimens who continued for a second year in the osteoporosis and metabolic substudy of the HOPE study, see Table 8.

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TABLE 7: INCIDENCE OF ENDOMETRIAL HYPERPLASIA/CANCER[a] AFTER ONE YEAR OF TREATMENT[b]

	----------Groups----------					
Patient	Prempro 0.625 mg/ 2.5 mg	Premarin 0.625 mg	Prempro 0.45 mg/ 1.5 mg	Premarin 0.45 mg	Prempro 0.3 mg/ 1.5 mg	Premarin 0.3 mg
Total number of patients	331	348	331	338	327	326
Number of patients with evaluable biopsies	278	249	272	279	271	269
No. (%) of patients with biopsies:						
• Hyperplasia/cancer[a] (consensus[c])	0 (0)[d]	20 (8)	1 (<1)[a,d]	9 (3)	1 (<1)[e]	1 (<1)[a]

[a] All cases of hyperplasia/cancer were endometrial hyperplasia, except for 1 patient in the Premarin 0.3 mg group diagnosed with endometrial cancer based on endometrial biopsy and 1 patient in the Premarin/MPA 0.45 mg/1.5 mg group diagnosed with endometrial cancer based on endometrial biopsy.
[b] Two (2) primary pathologists evaluated each endometrial biopsy. Where there was lack of agreement on the presence or absence of hyperplasia/cancer between the two, a third pathologist adjudicated (consensus).
[c] For an endometrial biopsy to be counted as consensus endometrial hyperplasia or cancer, at least 2 pathologists had to agree on the diagnosis.
[d] Significant ($p < 0.05$) in comparison with corresponding dose of Premarin alone.
[e] Non-significant in comparison with corresponding dose of Premarin alone.

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TABLE 8: OSTEOPOROSIS AND METABOLIC SUBSTUDY, INCIDENCE OF ENDOMETRIAL HYPERPLASIA/CANCER[a] AFTER TWO YEARS OF TREATMENT[b]

	----------Groups----------					
Patient	Prempro 0.625 mg/ 2.5 mg	Premarin 0.625 mg	Prempro 0.45 mg/ 1.5 mg	Premarin 0.45 mg	Prempro 0.3 mg/ 1.5 mg	Premarin 0.3 mg
Total number of patients	75	65	75	74	79	73
Number of patients with evaluable biopsies	62	55	69	67	75	63
No. (%) of patients with biopsies:						
• Hyperplasia/cancer[a] (consensus[c])	0 (0)[d]	15 (27)	0 (0)[d]	10 (15)	0 (0)[d]	2 (3)

[a] All cases of hyperplasia/cancer were endometrial hyperplasia in patients who continued for a second year in the osteoporosis and metabolic substudy of the HOPE study.
[b] Two (2) primary pathologists evaluated each endometrial biopsy. Where there was lack of agreement on the presence or absence of hyperplasia/cancer between the two, a third pathologist adjudicated (consensus).
[c] For an endometrial biopsy to be counted as consensus endometrial hyperplasia or cancer, at least 2 pathologists had to agree on the diagnosis.
[d] Significant ($p < 0.05$) in comparison with corresponding dose of Premarin alone.

14.4 Effects on Uterine Bleeding or Spotting

The effects of PREMPRO on uterine bleeding or spotting, as recorded on daily diary cards, were evaluated in 2 clinical trials. Results are shown in Figures 1 and 2.

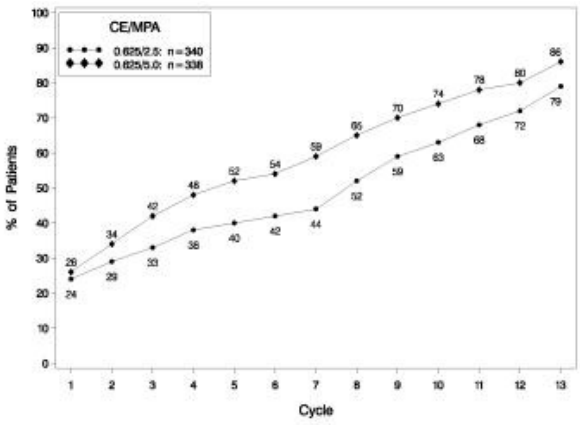

FIGURE 1. PATIENTS WITH CUMULATIVE AMENORRHEA OVER TIME PERCENTAGES OF WOMEN WITH NO BLEEDING OR SPOTTING AT A GIVEN CYCLE THROUGH CYCLE 13 INTENT-TO-TREAT POPULATION, LOCF

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Note: The percentage of patients who were amenorrheic in a given cycle and through cycle 13 is shown. If data were missing, the bleeding value from the last reported day was carried forward (LOCF).

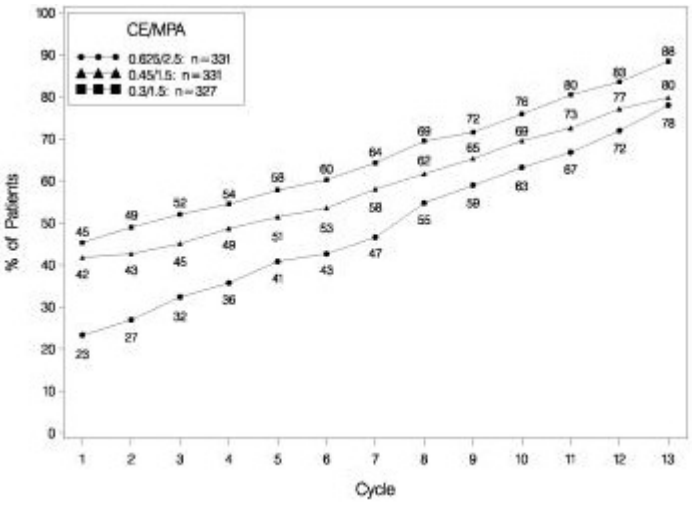

FIGURE 2. PATIENTS WITH CUMULATIVE AMENORRHEA OVER TIME PERCENTAGES OF WOMEN WITH NO BLEEDING OR SPOTTING AT A GIVEN CYCLE THROUGH CYCLE 13 INTENT-TO-TREAT POPULATION, LOCF

Note: The percentage of patients who were amenorrheic in a given cycle and through cycle 13 is shown. If data were missing, the bleeding value from the last reported day was carried forward (LOCF).

14.5 Effects on Bone Mineral Density

Health and Osteoporosis, Progestin and Estrogen (HOPE) Study

The HOPE study was a double-blind, randomized, placebo/active-drug-controlled, multicenter study of healthy postmenopausal women with an intact uterus. Subjects (mean age 53.3 ± 4.9 years) were 2.3 ± 0.9 years on average since menopause and took one 600 mg tablet of elemental calcium (Caltrate™) daily. Subjects were not given Vitamin D supplements. They were treated with PREMPRO 0.625 mg/2.5 mg, 0.45 mg/1.5 mg or 0.3 mg/1.5 mg, comparable doses of Premarin alone, or placebo. Prevention of bone loss was assessed by measurement of bone mineral density (BMD), primarily at the anteroposterior lumbar spine (L_2 to L_4). Secondarily, BMD measurements of the total body, femoral neck, and trochanter were also analyzed. Serum osteocalcin, urinary calcium, and N-telopeptide were used as bone turnover markers (BTM) at cycles 6, 13, 19, and 26.

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Intent-to-treat subjects

All active treatment groups showed significant differences from placebo in each of the four BMD endpoints. These significant differences were seen at cycles 6, 13, 19, and 26.

The percent changes from baseline to final evaluation are shown in Table 9.

TABLE 9: PERCENT CHANGE IN BONE MINERAL DENSITY: COMPARISON BETWEEN ACTIVE AND PLACEBO GROUPS IN THE INTENT-TO-TREAT POPULATION, LOCF

Region Evaluated Treatment Group[a]	No. of Subjects	Baseline (g/cm^2) Mean ± SD	Change from Baseline (%) Adjusted Mean ± SE	p-Value vs. Placebo
L_2 to L_4 BMD				
0.625/2.5	81	1.14 ± 0.16	3.28 ± 0.37	<0.001
0.45/1.5	89	1.16 ± 0.14	2.18 ± 0.35	<0.001
0.3/1.5	90	1.14 ± 0.15	1.71 ± 0.35	<0.001
Placebo	85	1.14 ± 0.14	-2.45 ± 0.36	
Total body BMD				
0.625/2.5	81	1.14 ± 0.08	0.87 ± 0.17	<0.001
0.45/1.5	89	1.14 ± 0.07	0.59 ± 0.17	<0.001
0.3/1.5	91	1.13 ± 0.08	0.60 ± 0.16	<0.001
Placebo	85	1.13 ± 0.08	-1.50 ± 0.17	
Femoral neck BMD				
0.625/2.5	81	0.89 ± 0.14	1.62 ± 0.46	<0.001
0.45/1.5	89	0.89 ± 0.12	1.48 ± 0.44	<0.001
0.3/1.5	91	0.86 ± 0.11	1.31 ± 0.43	<0.001
Placebo	85	0.88 ± 0.14	-1.72 ± 0.45	
Femoral trochanter BMD				
0.625/2.5	81	0.77 ± 0.14	3.35 ± 0.59	0.002
0.45/1.5	89	0.76 ± 0.12	2.84 ± 0.57	0.011
0.3/1.5	91	0.76 ± 0.12	3.93 ± 0.56	<0.001
Placebo	85	0.75 ± 0.12	0.81 ± 0.58	

[a] Identified by dosage (mg/mg) of Premarin/MPA or placebo.

Figure 3 shows the cumulative percentage of subjects with percent changes from baseline in spine BMD equal to or greater than the percent change shown on the x-axis.

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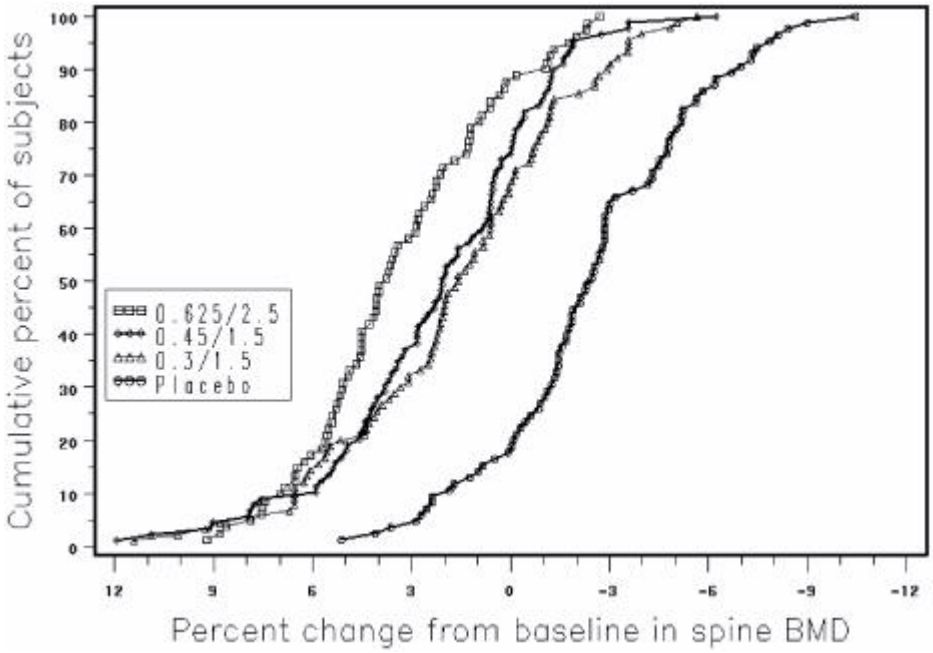

FIGURE 3. CUMULATIVE PERCENT OF SUBJECTS WITH CHANGES FROM BASELINE IN SPINE BMD OF GIVEN MAGNITUDE OR GREATER IN PREMARIN/MPA AND PLACEBO GROUPS

The mean percent changes from baseline in L_2 to L_4 BMD for women who completed the bone density study are shown with standard error bars by treatment group in Figure 4. Significant differences between each of the PREMPRO dosage groups and placebo were found at cycles 6, 13, 19, and 26.

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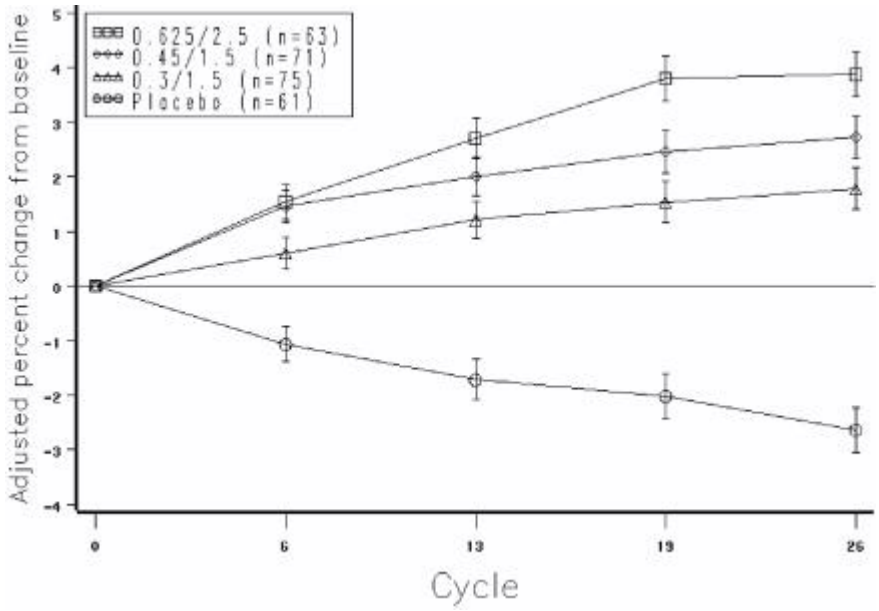

FIGURE 4. ADJUSTED MEAN (SE) PERCENT CHANGE FROM BASELINE AT EACH CYCLE IN SPINE BMD: SUBJECTS COMPLETING IN PREMARIN/MPA GROUPS AND PLACEBO

The bone turnover markers, serum osteocalcin and urinary N-telopeptide, significantly decreased ($p < 0.001$) in all active-treatment groups at cycles 6, 13, 19, and 26 compared with the placebo group. Larger mean decreases from baseline were seen with the active groups than with the placebo group. Significant differences from placebo were seen less frequently in urine calcium; only with PREMPRO 0.625 mg/2.5 mg and 0.45 mg/1.5 mg were there significantly larger mean decreases than with placebo at 3 or more of the 4 time points.

14.6 Women's Health Initiative Studies

The WHI enrolled approximately 27,000 predominantly healthy postmenopausal women in two substudies to assess the risks and benefits of daily oral CE (0.625 mg)-alone or in combination with MPA (2.5 mg) compared to placebo in the prevention of certain chronic diseases. The primary endpoint was the incidence of CHD (defined as nonfatal MI, silent MI and CHD death), with invasive breast cancer as the primary adverse outcome. A "global index" included the earliest occurrence of CHD, invasive breast cancer, stroke, PE, endometrial cancer (only in the CE plus MPA substudy), colorectal cancer, hip fracture, or death due to other causes. These substudies did not evaluate the effects of CE plus MPA or CE-alone on menopausal symptoms.

WHI Estrogen Plus Progestin Substudy

The WHI estrogen plus progestin substudy was stopped early. According to the predefined stopping rule, after an average follow-up of 5.6 years of treatment, the increased risk of invasive breast cancer and cardiovascular events exceeded the specified benefits included in the "global

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index." The absolute excess risk of events included in the "global index" was 19 per 10,000 women-years.

For those outcomes included in the WHI "global index" that reached statistical significance after 5.6 years of follow-up, the absolute excess risks per 10,000 women-years in the group treated with CE plus MPA were 7 more CHD events, 8 more strokes, 10 more PEs, and 8 more invasive breast cancers, while the absolute risk reductions per 10,000 women-years were 6 fewer colorectal cancers and 5 fewer hip fractures.

Results of the CE plus MPA substudy, which included 16,608 women (average 63 years of age, range 50 to 79; 83.9 percent White, 6.8 percent Black, 5.4 percent Hispanic, 3.9 percent Other) are presented in Table 10. These results reflect centrally adjudicated data after an average follow-up of 5.6 years.

TABLE 10: Relative and Absolute Risk Seen in the Estrogen Plus Progestin Substudy of WHI at an Average of 5.6 Years[a,b]

Event	Relative Risk CE/MPA vs. Placebo (95% nCI[c])	CE/MPA n = 8,506	Placebo n = 8,102
		Absolute Risk per 10,000 Women-Years	
CHD events	1.23 (0.99–1.53)	41	34
Non-fatal MI	*1.28 (1.00–1.63)*	*31*	*25*
CHD death	*1.10 (0.70–1.75)*	*8*	*8*
All Strokes	1.31 (1.03–1.68)	33	25
Ischemic stroke	*1.44 (1.09–1.90)*	*26*	*18*
Deep vein thrombosis[d]	1.95 (1.43–2.67)	26	13
Pulmonary embolism	2.13 (1.45–3.11)	18	8
Invasive breast cancer[e]	1.24 (1.01–1.54)	41	33
Colorectal cancer	0.61 (0.42–0.87)	10	16
Endometrial cancer[d]	0.81 (0.48–1.36)	6	7
Cervical cancer[d]	1.44 (0.47–4.42)	2	1
Hip fracture	0.67 (0.47–0.96)	11	16
Vertebral fractures[d]	0.65 (0.46–0.92)	11	17

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TABLE 10: Relative and Absolute Risk Seen in the Estrogen Plus Progestin Substudy of WHI at an Average of 5.6 Years[a,b]

Event	Relative Risk CE/MPA vs. Placebo (95% nCI[c])	CE/MPA n = 8,506	Placebo n = 8,102
		Absolute Risk per 10,000 Women-Years	
Lower arm/wrist fractures[d]	0.71 (0.59–0.85)	44	62
Total fractures[d]	0.76 (0.69–0.83)	152	199
Overall Mortality[f]	1.00 (0.83-1.19)	52	52
Global Index[g]	1.13 (1.02-1.25)	184	165

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

Timing of the initiation of estrogen plus progestin 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 to 59 years of age, a non-significant trend toward reduced risk for overall mortality *[hazard ratio (HR) 0.69 (95 percent CI, 0.44-1.07)]*.

WHI Estrogen-Alone Substudy

The WHI estrogen-alone substudy was stopped early because an increased risk of stroke was observed, and it was deemed that no further information would be obtained regarding the risks and benefits of estrogen-alone in predetermined primary endpoints.

Results of the estrogen-alone substudy, which included 10,739 women (average 63 years of age, range 50 to 79; 75.3 percent White, 15.1 percent Black, 6.1 percent Hispanic, 3.6 percent Other) after an average follow-up of 7.1 years, are presented in Table 11.

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Table 11: Relative and Absolute Risk Seen in the Estrogen-Alone Substudy of WHI[a]

Event	Relative Risk CE vs. Placebo (95% nCI[b])	CE n = 5,310	Placebo n = 5,429
		Absolute Risk per 10,000 Women-Years	
CHD events[c]	0.95 (0.78–1.16)	54	57
Non-fatal MI[c]	*0.91 (0.73–1.14)*	*40*	*43*
CHD death[c]	*1.01 (0.71–1.43)*	*16*	*16*
All Strokes[c]	1.33 (1.05–1.68)	45	33
Ischemic stroke[c]	*1.55 (1.19–2.01)*	*38*	*25*
Deep vein thrombosis[c,d]	1.47 (1.06–2.06)	23	15
Pulmonary embolism[c]	1.37 (0.90–2.07)	14	10
Invasive breast cancer[c]	0.80 (0.62–1.04)	28	34
Colorectal cancer[e]	1.08 (0.75–1.55)	17	16
Hip fracture[c]	0.65 (0.45–0.94)	12	19
Vertebral fractures[c,d]	0.64 (0.44–0.93)	11	18
Lower arm/wrist fractures[c,d]	0.58 (0.47–0.72)	35	59
Total fractures[c,d]	0.71 (0.64–0.80)	144	197
Death due to other causes[e,f]	1.08 (0.88–1.32)	53	50
Overall mortality[c,d]	1.04 (0.88–1.22)	79	75
Global Index[g]	1.02 (0.92–1.13)	206	201

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

For those outcomes included in the WHI "global index" that reached statistical significance, the absolute excess risk per 10,000 women-years in the group treated with CE-alone was 12 more strokes while the absolute risk reduction per 10,000 women-years was 7 fewer hip fractures.[9] The absolute excess risk of events included in the "global index" was a non-significant 5 events per 10,000 women-years. There was no difference between the groups in terms of all-cause mortality.

No overall difference for primary CHD events (nonfatal MI, silent MI and CHD death) and invasive breast cancer incidence in women receiving CE-alone compared with placebo was

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reported in final centrally adjudicated results from the estrogen-alone substudy, after an average follow up of 7.1 years.

Centrally adjudicated results for stroke events from the estrogen-alone substudy, after an average follow-up of 7.1 years, reported no significant difference in distribution of stroke subtype or severity, including fatal strokes, in women receiving CE-alone compared to placebo. Estrogen-alone increased the risk for ischemic stroke, and this excess risk was present in all subgroups of women examined.[10]

Timing of the initiation of estrogen-alone therapy relative to the start of menopause may affect the overall risk benefit profile. The WHI estrogen-alone substudy, stratified by age, showed in women 50 to 59 years of age a non-significant trend toward reduced risk for CHD [HR 0.63 (95 percent CI, 0.36-1.09)] and overall mortality *[HR 0.71 (95 percent CI, 0.46-1.11)]*.

14.7 Women's Health Initiative Memory Study

The WHIMS estrogen plus progestin ancillary study of WHI enrolled 4,532 predominantly healthy postmenopausal women 65 years of age and older (47 percent were 65 to 69 years of age; 35 percent were 70 to 74 years of age; and 18 percent were 75 years of age and older) to evaluate the effects of daily CE (0.625 mg) plus MPA (2.5 mg) on the incidence of probable dementia (primary outcome) compared to placebo.

After an average follow-up of 4 years, the relative risk of probable dementia for CE plus MPA versus placebo was 2.05 (95 percent CI, 1.21-3.48). The absolute risk of probable dementia for CE plus MPA versus placebo was 45 versus 22 cases per 10,000 women-years. Probable dementia as defined in this study included Alzheimer's disease (AD), vascular dementia (VaD) and mixed types (having features of both AD and VaD). The most common classification of probable dementia in the treatment group and the placebo group was AD. Since the ancillary study was conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women *[see Warnings and Precautions (5.3), and Use in Specific Populations (8.5)]*.

The WHIMS estrogen-alone ancillary study of WHI enrolled 2,947 predominantly healthy hysterectomized postmenopausal women 65 to 79 years of age and older (45 percent were 65 to 69 years of age; 36 percent were 70 to 74 years of age; 19 percent were 75 years of age and older) to evaluate the effects of daily CE (0.625 mg)-alone on the incidence of probable dementia (primary outcome) compared to placebo.

After an average follow-up of 5.2 years, the relative risk of probable dementia for CE-alone versus placebo was 1.49 (95 percent CI, 0.83-2.66). The absolute risk of probable dementia for CE-alone versus placebo was 37 versus 25 cases per 10,000 women-years. Probable dementia as defined in this study included AD, VaD and mixed types (having features of both AD and VaD). The most common classification of probable dementia in the treatment group and the placebo group was AD. Since the ancillary study was conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women *[see Warnings and Precautions (5.3), and Use in Specific Populations (8.5)]*.

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When data from the two populations were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.76 (95 percent CI, 1.19-2.60). Differences between groups became apparent in the first year of treatment. It is unknown whether these findings apply to younger postmenopausal women *[see Warnings and Precautions (5.3), and Use in Specific Populations (8.5)]*.

15 REFERENCES

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4. Curb JD, et al. Venous Thrombosis and Conjugated Equine Estrogen in Women Without a Uterus. *Arch Int Med*. 2006;166:772-780.
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16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

PREMPRO therapy consists of a single tablet to be taken once daily.

PREMPRO 0.3 mg/1.5 mg

NDC 0046-1105-11, carton includes 1 blister card containing 28 oval, cream tablets.

PREMPRO 0.45 mg/1.5 mg

NDC 0046-1106-11, carton includes 1 blister card containing 28 oval, gold tablets.

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PREMPRO 0.625 mg/2.5 mg

NDC 0046-1107-11, carton includes 1 blister card containing 28 oval, peach tablets.

PREMPRO 0.625 mg/5 mg

NDC 0046-1108-11, carton includes 1 blister card containing 28 oval, light-blue tablets.

PREMPHASE therapy consists of two separate tablets; one maroon Premarin tablet taken daily on days 1 through 14 and one light-blue tablet taken on days 15 through 28.

NDC 0046-2575-12, carton includes 1 blister card containing 28 tablets (14 oval, maroon Premarin tablets and 14 oval, light-blue tablets).

The appearance of PREMPRO tablets is a trademark of Pfizer Inc.

The appearance of PREMARIN tablets is a trademark of Pfizer Inc. The appearance of the conjugated estrogens/medroxyprogesterone acetate combination tablets is a trademark.

16.2 Storage and Handling

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling.

17.1 Abnormal Vaginal Bleeding

Inform postmenopausal women of the importance of reporting abnormal vaginal bleeding to their healthcare provider as soon as possible *[see Warnings and Precautions (5.2)]*.

17.2 Possible Serious Adverse Reactions with Estrogen Plus Progestin Therapy

Inform postmenopausal women of possible serious adverse reactions of estrogen plus progestin therapy including Cardiovascular Disorders, Malignant Neoplasms, and Probable Dementia *[see Warnings and Precautions (5.1, 5.2, 5.3)]*.

17.3 Possible Less Serious but Common Adverse Reactions with Estrogen Plus Progestin Therapy

Inform postmenopausal women of possible less serious but common adverse reactions of estrogen plus progestin therapy such as headache, breast pain and tenderness, nausea and vomiting.

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PATIENT INFORMATION

PREMPRO®
(Conjugated Estrogens/Medroxyprogesterone Acetate Tablets)
PREMPHASE®
(Conjugated Estrogens plus Medroxyprogesterone Acetate Tablets)

Read this PATIENT INFORMATION before you start taking PREMPRO or PREMPHASE and read what you get each time you refill your PREMPRO or PREMPHASE prescription. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about PREMPRO and PREMPHASE (combinations of estrogens and a progestin)?

- Do not use estrogens with progestins to prevent heart disease, heart attacks, strokes, or dementia (decline of brain function)
- Using estrogens with progestins may increase your chances of getting heart attacks, strokes, breast cancer, or blood clots
- Using estrogens with progestins may increase your chance of getting dementia, based on a study of women 65 years of age or older
- Do not use estrogen-alone to prevent heart disease, heart attacks, strokes or dementia
- Using estrogen-alone may increase your chance of getting cancer of the uterus (womb)
- Using estrogen-alone may increase your chances of getting strokes or blood clots
- Using estrogen-alone may increase your chance of getting dementia, based on a study of women 65 years of age or older
- You and your healthcare provider should talk regularly about whether you still need treatment with PREMPRO or PREMPHASE

What is PREMPRO or PREMPHASE?

PREMPRO or PREMPHASE are medicines that contain two kinds of hormones, estrogens and a progestin.

What is PREMPRO or PREMPHASE used for?

PREMPRO or PREMPHASE is used after menopause to:

- **Reduce moderate to severe hot flashes**

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Estrogens are hormones made by a woman's ovaries. The ovaries normally stop making estrogens when a woman is between 45 and 55 years old. This drop in body estrogen levels causes the "change of life" or menopause (the end of monthly menstrual periods). Sometimes, both ovaries are removed during an operation before natural menopause takes place. The sudden drop in estrogen levels causes "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.

- **Treat menopausal changes in and around the vagina**

  You and your healthcare provider should talk regularly about whether you still need treatment with PREMPRO or PREMPHASE to control these problems. If you use PREMPRO or PREMPHASE only to treat your menopausal changes in and around your vagina, talk with your healthcare provider about whether a topical vaginal product would be better for you.

- **Help reduce your chances of getting osteoporosis (thin weak bones)**

  Osteoporosis from menopause is a thinning of the bones that makes them weaker and easier to break. If you use PREMPRO or PREMPHASE only to prevent osteoporosis due to menopause, talk with your healthcare provider about whether a different treatment or medicine without estrogens might be better for you. Weight-bearing exercise, like walking or running, and taking calcium (1500 mg per day of elemental calcium) and vitamin D (400-800 IU per day) supplements may also lower your chances of getting postmenopausal osteoporosis. It is important to talk about exercise and supplements with your healthcare provider before starting them.

  You and your healthcare provider should talk regularly about whether you still need treatment with PREMPRO or PREMPHASE.

Who should not take PREMPRO or PREMPHASE?

Do not take PREMPRO or PREMPHASE if you have had your uterus (womb) removed (hysterectomy).

PREMPRO and PREMPHASE contain a progestin to decrease the chance of getting cancer of the uterus. If you do not have a uterus, you do not need a progestin and you should not take PREMPRO or PREMPHASE.

Do not take PREMPRO or PREMPHASE if you:

- **Have unusual vaginal bleeding**
- **Currently have or have had certain cancers**

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Estrogens may increase the chance of getting certain types of cancers, including cancer of the breast or uterus. If you have or have had cancer, talk with your healthcare provider about whether you should use PREMPRO or PREMPHASE.

- **Had a stroke or heart attack**
- **Currently have or have had blood clots**
- **Currently have or have had liver problems**
- **Have been diagnosed with a bleeding disorder**
- **Are allergic to PREMPRO or PREMPHASE or any of their ingredients**

  See the list of ingredients in PREMPRO and PREMPHASE at the end of this leaflet.

- **Think you may be pregnant**

Tell your healthcare provider

- **If you have any unusual vaginal bleeding**

  Vaginal bleeding after menopause may be a warning sign of cancer of the uterus (womb). Your healthcare provider should check any unusual vaginal bleeding to find out the cause.

- **About all of your medical problems**

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

- **About all the medicines you take**

  This includes prescription and nonprescription medicines, vitamins, and herbal supplements. Some medicines may affect how PREMPRO or PREMPHASE works. PREMPRO or PREMPHASE may also affect how your other medicines work.

- **If you are going to have surgery or will be on bedrest**

  You may need to stop taking PREMPRO or PREMPHASE.

- **If you are breastfeeding**

  The hormones in PREMPRO and PREMPHASE can pass into your breast milk.

How should I take PREMPRO or PREMPHASE?

- Take one PREMPRO or PREMPHASE tablet at the same time each day

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- 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.

- 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 PREMPRO or PREMPHASE.

What are the possible side effects of PREMPRO or PREMPHASE?

Side effects are grouped by how serious they are and how often they happen when you are treated.

Serious, but less common side effects include:

- Heart attack
- Stroke
- Blood clots
- Dementia
- Breast cancer
- Cancer of the lining of the uterus (womb)
- Cancer of the ovary
- High blood pressure
- High blood sugar
- Gallbladder disease
- Liver problems
- Enlargement of benign tumors of the uterus (“fibroids”)
- Mental depression
- Severe allergic reaction

Call your healthcare provider right away if you get any of the following warning signs or any other unusual symptoms that concern you:

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- New breast lumps
- Unusual vaginal bleeding
- Changes in vision or speech
- Sudden new severe headaches
- Severe pains in your chest or legs with or without shortness of breath, weakness and fatigue
- Swollen lips, tongue and face

Less serious, but common side effects include:

- Headache
- Breast pain
- Irregular vaginal bleeding or spotting
- Stomach or abdominal cramps, bloating
- Nausea and vomiting
- Hair loss
- Fluid retention
- Vaginal yeast infection

These are not all the possible side effects of PREMPRO or PREMPHASE. For more information, ask your healthcare provider or pharmacist for advice about side effects. You may report side effects to Pfizer Inc. at 1-800-438-1985 or to FDA at 1-800-FDA-1088.

What can I do to lower my chances of getting a serious side effect with PREMPRO or PREMPHASE?

- Talk with your healthcare provider regularly about whether you should continue taking PREMPRO or PREMPHASE
- See your healthcare provider right away if you get vaginal bleeding while taking PREMPRO or PREMPHASE
- Have a pelvic exam, breast exam and mammogram (breast X-ray) every year unless your healthcare provider tells you something else

  If members of your family have had breast cancer or if you have ever had breast lumps or an abnormal mammogram, you may need to have breast exams more often.

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- If you have high blood pressure, high cholesterol (fat in the blood), diabetes, are overweight, or if you use tobacco, you may have higher chances for getting heart disease

  Ask your healthcare provider for ways to lower your chances of getting heart disease.

General Information about the safe and effective use of PREMPRO and PREMPHASE

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

Keep PREMPRO and PREMPHASE out of the reach of children.

This leaflet provides a summary of the most important information about PREMPRO and PREMPHASE. If you would like more information, talk with your healthcare provider or pharmacist. You can ask for information about PREMPRO and PREMPHASE that is written for health professionals.

What are the ingredients in PREMPRO and PREMPHASE?

PREMPRO contains the same conjugated estrogens found in Premarin, which are a mixture of sodium estrone sulfate and sodium equilin sulfate and other components, including sodium sulfate conjugates, 17α-dihydroequilin, 17α-estradiol and 17β-dihydroequilin. PREMPRO also contains either 1.5, 2.5, or 5 mg of medroxyprogesterone acetate.

PREMPRO 0.3 mg/1.5 mg and 0.45 mg/1.5 mg tablets also contain calcium phosphate tribasic, microcrystalline cellulose, lactose monohydrate, carnauba wax, hypromellose, magnesium stearate, polyethylene glycol, sucrose, hydroxypropyl cellulose, Eudragit NE 30D, titanium dioxide, yellow iron oxide, propylene glycol and black iron oxide.

PREMPRO 0.625 mg/2.5 mg tablets also contain calcium phosphate tribasic, microcrystalline cellulose, lactose monohydrate, hypromellose, magnesium stearate, polyethylene glycol, sucrose, hydroxypropyl cellulose, Eudragit NE 30D, povidone, titanium dioxide, red iron oxide, yellow iron oxide, and black iron oxide.

PREMPRO 0.625 mg/5 mg tablets also contain calcium phosphate tribasic, carnauba wax, Eudragit NE 30D, hydroxypropyl_cellulose, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sucrose, titanium dioxide, FD&C Blue No. 2, and black iron oxide.

PREMPHASE is two separate tablets. One tablet (maroon color) is 0.625 mg of Premarin, which is a mixture of sodium estrone sulfate and sodium equilin sulfate and other components, including sodium sulfate conjugates, 17 α-dihydroequilin, 17 α-estradiol and 17 β-dihydroequilin. The maroon tablet also contains calcium phosphate tribasic, hydroxypropyl cellulose, microcrystalline cellulose, powdered cellulose, hypromellose, lactose monohydrate, magnesium stearate, polyethylene glycol, sucrose, titanium dioxide, FD&C Blue No. 2, FD&C Red No. 40. The second tablet (light-blue color) contains 0.625 mg of the same ingredients as

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the maroon color tablet plus 5 mg of medroxyprogesterone acetate. The light-blue tablet also contains calcium phosphate tribasic, carnauba wax, Eudragit NE 30D, hydroxypropyl cellulose, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sucrose, titanium dioxide, FD&C Blue No. 2, and black iron oxide.

PREMPRO therapy consists of a single tablet to be taken once daily.

PREMPRO 0.3 mg/1.5 mg

Blister Card - Each carton includes 1 blister card containing 28 oval, cream tablets. Each tablet contains 0.3 mg of the conjugated estrogens found in Premarin tablets and 1.5 mg of medroxyprogesterone acetate for oral administration.

PREMPRO 0.45 mg/1.5 mg

Blister Card - Each carton includes 1 blister card containing 28 oval, gold tablets. Each tablet contains 0.45 mg of the conjugated estrogens found in Premarin tablets and 1.5 mg of medroxyprogesterone acetate for oral administration.

PREMPRO 0.625 mg/2.5 mg

Blister Card - Each carton includes 1 blister card containing 28 oval, peach tablets. Each tablet contains 0.625 mg of the conjugated estrogens found in Premarin tablets and 2.5 mg of medroxyprogesterone acetate for oral administration.

PREMPRO 0.625 mg/5 mg

Blister Card - Each carton includes 1 blister card containing 28 oval, light-blue tablets. Each tablet contains 0.625 mg of the conjugated estrogens found in Premarin tablets and 5 mg of medroxyprogesterone acetate for oral administration.

PREMPHASE therapy consists of two separate tablets; one maroon Premarin tablet taken daily on days 1 through 14 and one light-blue tablet taken on days 15 through 28.

Each carton includes 1 blister pack containing 28 tablets. One blister pack contains 14 oval, maroon Premarin tablets containing 0.625 mg of conjugated estrogens and 14 oval, light-blue tablets that contain 0.625 mg of the conjugated estrogens found in Premarin tablets and 5 mg of medroxyprogesterone acetate for oral administration.

The appearance of PREMPRO tablets is a trademark of Pfizer Inc.

The appearance of PREMARIN tablets is a trademark of Pfizer Inc. The appearance of the conjugated estrogens/medroxyprogesterone acetate combination tablets is a trademark.

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

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