

PREFEST[®] (estradiol/norgestimate) tablets

Rx only

PHYSICIAN'S PACKAGE INSERT

WARNING

Estrogens and progestins should not be used for the prevention of cardiovascular disease. (See **WARNINGS, Cardiovascular disorders.**)

The Women's Health Initiative (WHI) study reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women (50 to 79 years of age) during 5 years of treatment with oral conjugated estrogens (CE 0.625 mg) combined with medroxyprogesterone acetate (MPA 2.5 mg) relative to placebo. (See **CLINICAL PHARMACOLOGY, Clinical Studies.**)

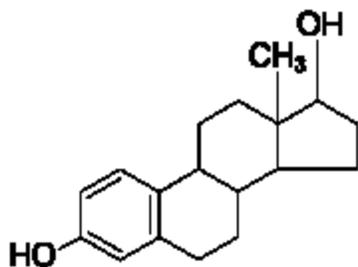
The Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, reported increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with oral conjugated estrogens plus medroxyprogesterone acetate relative to placebo. It is unknown whether this finding applies to younger postmenopausal women or to women taking estrogen alone therapy. (See **CLINICAL PHARMACOLOGY, Clinical Studies.**)

Other doses of oral conjugated estrogens with medroxyprogesterone acetate, and other combinations and dosage forms of estrogens and progestins were not studied in the WHI clinical trials and, in the absence of comparable data, these risks should be assumed to be similar. Because of these risks, 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.

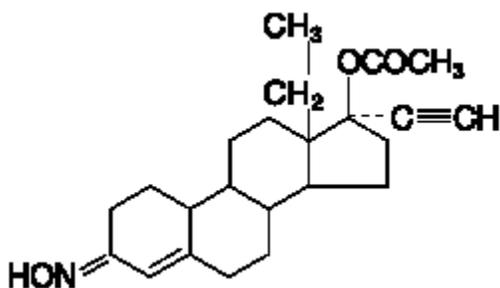
Description

The PREFEST regimen provides for a single oral tablet to be taken once daily. The pink tablet containing 1.0 mg estradiol is taken on days one through three of therapy; the white tablet containing 1.0 mg estradiol and 0.09 mg norgestimate is taken on days four through six of therapy. This pattern is then repeated continuously to produce the constant estrogen/intermittent progestogen regimen of PREFEST.

The estrogenic component of PREFEST is estradiol, USP. It is a white, crystalline solid, chemically described as estra-1,3,5(10)-triene-3,17 β -diol. It has an empirical formula of C₁₈H₂₄O₂ and molecular weight of 272.39. The structural formula is:



The progestational component of PREFEST is micronized norgestimate, a white powder which is chemically described as 18,19-dinor-17-pregn-4-en-20-yn-3-one, 17-(acetyloxy)-13-ethyl-,oxime,(17 α)-(+)-. It has an empirical formula of C₂₃H₃₁NO₃ and a molecular weight of 369.50. The structural formula is:



Each tablet for oral administration contains 1.0 mg estradiol alone or 1.0 mg estradiol and 0.09 mg of norgestimate, and the following inactive ingredients: croscarmellose sodium, microcrystalline cellulose, magnesium stearate, ferric oxide red, and lactose monohydrate.

Clinical Pharmacology

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

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

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

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

Norgestimate is a derivative of 19-nortestosterone and binds to androgen and progestogen receptors, similar to that of the natural hormone progesterone; it does not bind to estrogen receptors. Progestins counter the estrogenic effects by decreasing the number of nuclear estradiol receptors and suppressing epithelial DNA synthesis in endometrial tissue.

Pharmacokinetics

Absorption

Estradiol reaches its peak serum concentration (C_{max}) at approximately 7 hours in postmenopausal women receiving PREFEST (*Table 1*). Norgestimate is completely metabolized; its primary active metabolite, 17-deacetylnorgestimate, reaches C_{max} at approximately 2 hours after dose (*Table 1*). Upon co-administration of PREFEST with a high fat meal, the C_{max} values for estrone and estrone sulfate were increased by 14% and 24%, respectively, and the C_{max} for 17-deacetylnorgestimate was decreased by 16%. The AUC values for these analytes were not significantly affected by food.

Distribution

The distribution of exogenous estrogens is similar to that of endogenous estrogens. Estrogens are widely distributed in the body and are generally found in higher concentrations in the sex hormone target organs. Estrogens circulate in the blood largely bound to sex hormone binding globulin (SHBG) and albumin. 17-deacetylnorgestimate, the primary active metabolite of norgestimate, does not bind to SHBG, but to other serum proteins. The percent protein binding of 17-deacetylnorgestimate is approximately 99%.

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 the 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 gut followed by reabsorption. In postmenopausal women, a significant portion of the circulating estrogens exist as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogens. Norgestimate is extensively metabolized by first-pass mechanisms in the gastrointestinal tract and/or liver. Norgestimate's primary active metabolite is 17-deacetylnorgestimate.

Excretion

Estradiol, estrone, and estriol are excreted in the urine along with glucuronide and sulfate conjugates. Norgestimate metabolites are eliminated in the urine and feces. The half-life (t_{1/2}) of estradiol and 17-deacetylnorgestimate in postmenopausal women receiving PREFEST is approximately 16 and 37 hours, respectively.

Drug 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 preparations (*Hypericum perforatum*), 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.

Results of a subset population (n=24) from a clinical study conducted in 36 healthy postmenopausal women indicated that the steady state serum estradiol levels during the estradiol plus norgestimate phase of the regimen may be lower by 12-18% as compared with estradiol administered alone. The serum estrone levels may decrease by 4% and the serum estrone sulfate levels may increase by 17% during the estradiol plus norgestimate phase as compared with estradiol administered alone. The clinical relevance of these observations is unknown.

Special Populations

Race and body weight

The effects of race and body weight on the pharmacokinetics of estradiol, norgestimate, and their metabolites were evaluated in 164 healthy postmenopausal women (100 Caucasians, 61 Hispanics, 2 Blacks, and 1 Asian). No significant pharmacokinetic difference was observed between the Caucasian and the Hispanic postmenopausal women. No significant difference due to body weight was observed in women in the 60 to 80 kg weight range. Women with body weight higher than 80 kg, however, had approximately 40% lower peak serum levels of 17-deacetylnorgestimate, 30% lower AUC values for 17-deacetylnorgestimate and 30% lower C_{max} values for norgestrel. The clinical relevance of these observations is unknown.

No pharmacokinetic studies were conducted in other special populations.

Table 1: MEAN PHARMACOKINETIC PARAMETERS OF E₂, E₁, E₁S AND 17d-NGM^a FOLLOWING SINGLE AND MULTIPLE DOSING OF PREFEST

Analyte	Parameter ^b	Units	First Dose E ₂	First Dose E ₂ /NGM	Multiple Dose E ₂	Multiple Dose E ₂ /NGM
E ₂	C _{max}	pg/mL	27.4	39.3	49.7	46.2
	t _{max}	h	7	7	7	7
	AUC(0-24 h)	pg. h/mL	424	681	864	779
E ₁	C _{max}	pg/mL	210	285	341	325
	t _{max}	h	6	6	7	6
	AUC (0-24 h)	pg. h/mL	2774	4153	5429	4957
E ₁ S	C _{max}	ng/mL	11.0	13.9	14.9	14.5
	t _{max}	h	5	4	6	5
	AUC (0-24 h)	ng. h/mL	135	180	198	198
17d-NGM	C _{max}	pg/mL	NA ^c	515	NA	643
	t _{max}	h	NA	2	NA	2
	AUC (0-24 h)	pg. h/mL	NA	2146	NA	5322
	t _{1/2}	h	NA	37	NA	NA

- a) E₂ = Estradiol, E₁ = Estrone, E₁S = Estrone Sulfate, 17d-MGM = 17 -deacetylnorgestimate. Baseline uncorrected data are reported for E₂, E₁ and E₁S.
b) C_{max} = peak serum concentration, t_{max} = time to reach peak serum concentration, AUC (0-24 h) = area under serum concentration vs. time curve from 0 to 24 hours after dose, t_{1/2} = half-life.
c) NA = Not available or not applicable.

Clinical Studies

Effects on vasomotor symptoms

The effect of the estrogen component of PREFEST on vasomotor symptoms was confirmed in a 12-week placebo controlled trial of 168 healthy postmenopausal women between 28 and 66 years of age (87% Caucasian) with moderate to severe vasomotor symptoms (MSVS). The addition of norgestimate to estrogen (i.e., the PREFEST regimen) was studied in two 12-month trials in 1212 healthy postmenopausal women between 40 and 65 years of age (85% Caucasian) for endometrial protection. Results from a subset population (n=119) of these 12-month trials (women with MSVS) are shown in *Table 2*.

Table 2: CHANGE IN THE MEAN NUMBER OF MODERATE TO SEVERE VASOMOTOR SYMPTOMS (SUBSET OF SUBJECTS WITH 7 OR MORE MODERATE TO SEVERE HOT FLUSHES PER DAY)

	1 mg E ₂		PREFEST	
	N	Mean	N	Mean
Baseline	29	11.0	26	10.9
Week 4	29	3.3	26	2.6
Week 8	29	1.1	23	0.9
Week 12	29	1.1	23	0.7

The effects of the addition of norgestimate on steady state estrogen levels and the clinical relevance thereof have been discussed in **CLINICAL PHARMACOLOGY** (see **Drug Interactions**).

Effects on vulvar and vaginal atrophy

The effect of the estrogen component of PREFEST on vulvar and vaginal atrophy was confirmed in a 12-week placebo-controlled trial of healthy postmenopausal women with moderate to severe vasomotor symptoms (MSVS). The addition of norgestimate to estrogen (i.e., the PREFEST regimen) was studied in a 12-month trial in 143 healthy postmenopausal women between 42 and 65 years of age (92% Caucasian) for endometrial protection. Results from a subset population (n=69) with paired tests for maturation index of the vaginal mucosa are shown in *Table 3*.

Table 3: SUMMARY OF MATURATION INDEX RESULTS IN SUBJECTS WITH PAIRED TESTS FOLLOWING 7 MONTHS TREATMENT WITH PREFEST OR ESTRADIOL

	Pretreatment Mean	Month 7 Mean	Mean Change
1 mg Estradiol (N=37)			
Parabasal Cells (%)	25.1	2.7	-22.4
Intermediate Cells (%)	69.2	76.4	7.2
Superficial Cells (%)	5.7	20.9	15.3
PREFEST (N=32)			
Parabasal Cells (%)	31.9	0.0	-31.9
Intermediate Cells (%)	64.2	80.9	16.7
Superficial Cells (%)	3.9	19.1	15.2

Effects on the endometrium

The effect of PREFEST on the endometrium was evaluated in two 12-month trials. The combined results are shown in *Table 4*.

Table 4: INCIDENCE OF ENDOMETRIAL HYPERPLASIA AFTER 12 MONTHS OF TREATMENT (INTENT TO TREAT POPULATION)

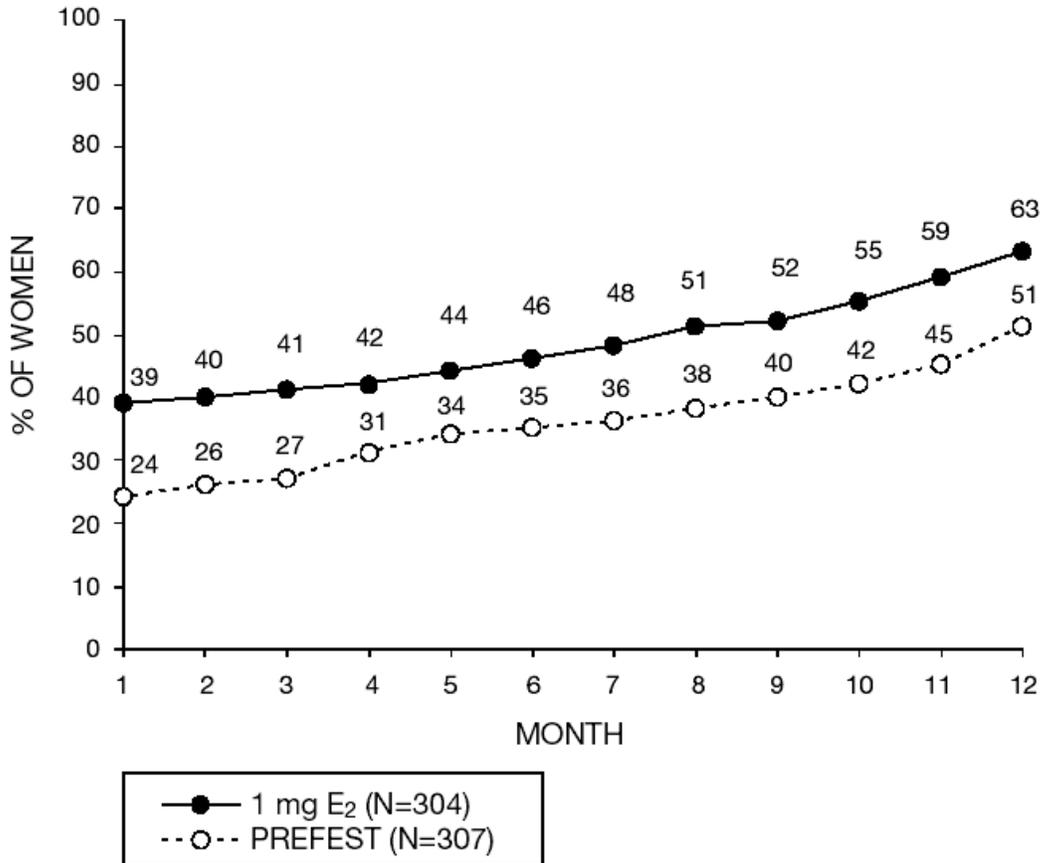
	Continuous 1 mg estradiol	PREFEST
Total No. Subjects	265	242
Total No. Evaluable Biopsies	256 (97%)	227 (94%)
Normal endometrium	182 (71%)	227 (100%)
Simple hyperplasia	64 (25%)	0 (0%)
Complex hyperplasia	2 (0.8%)	0 (0%)
Hyperplasia with cytological atypia	8 (3%)	0 (0%)

In another 12-month controlled clinical trial for endometrial protection an additional 190 postmenopausal women were treated with PREFEST. No subject had a diagnosis of endometrial hyperplasia after treatment.

Effects on uterine bleeding or spotting

The effects of PREFEST on uterine bleeding or spotting, as recorded on daily diary cards, were evaluated in two 12-month trials. Combined results are shown in *Figure 1*.

Figure 1: Subjects with Cumulative Amenorrhea Over Time (Percentage of Women With No Bleeding or Spotting At a Given Month Through Month 12), Intent to Treat Population



Effects on lipids

The effect of PREFEST on lipids was evaluated in a 12-month metabolic trial of healthy postmenopausal women. Results are shown in *Table 5*.

Table 5: EFFECTS ON LIPOPROTEINS AT MONTH 12

	1 mg E ₂		PREFEST	
	N	Change	N	Change
Total Cholesterol	36	1.2	31	-1.9
HDL	36	12.0	31	9.7
LDL	31	1.7	30	1.2
Triglycerides	36	29.0	31	9.4

Women's Health Initiative Studies

The Women's Health Initiative (WHI) enrolled a total of 27,000 predominantly healthy postmenopausal women to assess the risks and benefits of either the use of oral 0.625 mg conjugated estrogens (CE) per day alone or the use of oral 0.625 mg conjugated estrogens plus 2.5 mg medroxyprogesterone acetate (MPA) per day compared to placebo in the prevention of certain chronic diseases. The primary endpoint was the incidence of coronary heart disease (CHD) (nonfatal myocardial infarction and CHD death), with invasive breast cancer as the primary adverse outcome studied. A "global index" included the earliest occurrence of CHD, invasive breast cancer, stroke, pulmonary embolism (PE), endometrial cancer, colorectal cancer, hip fracture, or death due to other cause. The study did not evaluate the effects of CE or CE/MPA on menopausal symptoms.

The CE/MPA substudy was stopped early because, according to the predefined stopping rule, the increased risk of breast cancer and cardiovascular events exceeded the specified benefits included in the "global index." Results of the CE/MPA substudy, which included 16,608 women (average age of 63 years, range 50 to 79; 83.9% White, 6.5% Black, 5.5% Hispanic), after an average follow-up of 5.2 years are presented in *Table 6* below:

Table 6: RELATIVE AND ABSOLUTE RISK SEEN IN THE CE/MPA SUBSTORY OF WHI^a

Event ^c	Relative Risk CE/MPA vs placebo at 5.2 Years (95% CI ^e)	Placebo	CE/MPA
		N = 8102	N = 8506
		Absolute Risk per 10,000 Person-years	
CHD events	1.29 (1.02-1.63)	30	37
<i>Non-fatal MI</i>	<i>1.32 (1.02-1.72)</i>	23	30
<i>CHD death</i>	<i>1.18 (0.70-1.97)</i>	6	7
Invasive breast cancer ^b	1.26 (1.00-1.59)	30	38
Stroke	1.41 (1.09-1.85)	21	29
Pulmonary embolism	2.13 (1.39-3.25)	8	16
Colorectal cancer	0.63 (0.43-0.92)	16	10
Endometrial cancer	0.83 (0.47-1.47)	6	5
Hip fracture	0.66 (0.45-0.98)	15	10
Death due to causes other than the events above	0.92 (0.74-1.14)	40	37
Global Index ^c	1.15 (1.03-1.28)	151	170
Deep vein thrombosis ^d	2.07 (1.49-2.87)	13	26
Vertebral fractures ^d	0.66 (0.44-0.98)	15	9
Other osteoporotic fractures ^d	0.77 (0.69-0.86)	170	131

a) adapted from JAMA, 2002; 288:321-333

- b) includes metastatic and non-metastatic breast cancer with the exception of in situ breast cancer
- c) 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, endometrial cancer, colorectal cancer, hip fracture, or death due to other causes
- d) not included in Global Index
- e) nominal confidence intervals unadjusted for multiple looks and multiple comparisons

For those outcomes included in the “global index,” the absolute excess risks per 10,000 women-years in the group treated with CE/MPA were 7 more CHD events, 8 more strokes, 8 more PEs, and 8 more invasive breast cancers, while absolute risk reductions per 10,000 women-years were 6 fewer colorectal cancers and 5 fewer hip fractures. The absolute excess risk of events included in the “global index” was 19 per 10,000 women-years. There was no difference between the groups in terms of all-cause mortality. (See **BOXED WARNING, WARNINGS, and PRECAUTIONS.**)

Women’s Health Initiative Memory Study

The Women’s Health Initiative Memory Study (WHIMS), a substudy of WHI, enrolled 4,532 predominantly healthy postmenopausal women 65 years of age and older (47% were age 65 to 69 years, 35% were 70 to 74 years, and 18% were 75 years of age and older) to evaluate the effects of CE/MPA (0.625 mg conjugated estrogens plus 2.5 mg medroxyprogesterone acetate) on the incidence of probable dementia (primary outcome) compared with placebo.

After an average follow-up of 4 years, 40 women in the estrogen/progestin group (45 per 10,000 women-years) and 21 in the placebo group (22 per 10,000 women-years) were diagnosed with probable dementia. The relative risk of probable dementia in the hormone therapy group was 2.05 (95% CI, 1.21 to 3.48) compared to placebo. Differences between groups became apparent in the first year of treatment. It is unknown whether these findings apply to younger postmenopausal women. (See **BOXED WARNING and WARNINGS, Dementia.**)

Indications and Usage

PREFEST is indicated in women who have a uterus for the:

1. Treatment of moderate to severe vasomotor symptoms associated with the menopause.
2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribed solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.
3. Prevention of postmenopausal osteoporosis. 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.

The mainstays for decreasing the risk of postmenopausal osteoporosis are weight bearing exercise, adequate calcium and vitamin D intake, and when indicated, pharmacologic therapy. Postmenopausal women require an average of 1500 mg/day of elemental calcium. Therefore, when not contraindicated, calcium supplementation may be helpful for women with suboptimal

dietary intake. Vitamin D supplementation of 400-800 IU/day may also be required to ensure adequate daily intake in postmenopausal women.

Contraindications

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

1. Undiagnosed abnormal genital bleeding.
2. Known, suspected, or history of cancer of the breast.
3. Known or suspected estrogen-dependent neoplasia.
4. Active deep vein thrombosis, pulmonary embolism or history of these conditions.
5. Active or recent (e.g., within the past year) arterial thromboembolic disease (e.g., stroke, myocardial infarction).
6. Liver dysfunction or disease.
7. PREFEST should not be used in patients with known hypersensitivity to its ingredients.
8. Known or suspected pregnancy. There is no indication for PREFEST in pregnancy. There appears to be little or no increased risk of birth defects in children born to women who have used estrogens and progestins from oral contraceptives inadvertently during early pregnancy (See **PRECAUTIONS**).

Warnings

See **BOXED WARNINGS**.

1. Cardiovascular disorders.

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

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

a. Coronary heart disease and stroke.

In the Women's Health Initiative (WHI) study, an increase in the number of myocardial infarctions and strokes has been observed in women receiving CE compared to placebo. These observations are preliminary. (See **CLINICAL PHARMACOLOGY, Clinical Studies**.)

In the CE/MPA substudy of WHI, an increased risk of coronary heart disease (CHD) events (defined as nonfatal myocardial infarction and CHD death) was observed in women receiving CE/MPA compared to women receiving placebo (37 vs 30 per 10,000 women-years). The increase in risk was observed in year one and persisted.

In the same substudy of WHI, an increased risk of stroke was observed in women receiving CE/MPA compared to women receiving placebo (29 vs 21 per 10,000 women-years). The increase in risk was observed after the first year and persisted.

In postmenopausal women with documented heart disease (n=2,763, average age 66.7 years) a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/Progestin Replacement Study; HERS) treatment with CE/MPA (0.625mg/2.5mg per day) demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with CE/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/MPA-treated group than in the placebo group in year 1, but not during the subsequent years. Two thousand three hundred and twenty one 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/MPA group and the placebo group in HERS, HERS II, and overall.

Large doses of estrogen (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown in a large prospective clinical trial in men to increase the risks of nonfatal myocardial infarction, pulmonary embolism, and thrombophlebitis.

b. Venous thromboembolism (VTE).

In the Women's Health Initiative (WHI) study, an increase in VTE has been observed in women receiving CE compared to placebo. These observations are preliminary. (See **CLINICAL PHARMACOLOGY, Clinical Studies.**)

In the CE/MPA substudy of WHI, a 2-fold greater rate of VTE, including deep venous thrombosis and pulmonary embolism, was observed in women receiving CE/MPA compared to women receiving placebo. The rate of VTE was 34 per 10,000 women-years in the CE/MPA group compared to 16 per 10,000 women-years in the placebo group. The increase in VTE risk was observed during the first year and persisted.

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.

2. Malignant neoplasms.

a. Endometrial cancer.

The use of unopposed estrogens in women with intact uteri has been associated with an increased risk of endometrial cancer. The reported endometrial cancer risk among unopposed estrogen users is about 2- to 12-fold greater than in non-users, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with use of estrogens for less than one year. The greatest risk appears associated with prolonged use, with increased risks of 15- to 24-fold for five to ten 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 taking estrogen/progestin combinations is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be

undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. 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 has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.

b. Breast cancer.

The use of estrogens and progestins by postmenopausal women has been reported to increase the risk of breast cancer. The most important randomized clinical trial providing information about this issue is the Women's Health Initiative (WHI) substudy of CE/MPA (see **CLINICAL PHARMACOLOGY, Clinical Studies**). The results from observational studies are generally consistent with those of the WHI clinical trial and report no significant variation in the risk of breast cancer among different estrogens or progestins, doses, or routes of administration.

The CE/MPA substudy of WHI reported an increased risk of breast cancer in women who took CE/MPA for a mean follow-up of 5.6 years. Observational studies have also reported an increased risk for estrogen/progestin combination therapy, and a smaller increased risk for estrogen alone therapy, after several years of use. In the WHI trial and from observational studies, the excess risk increased with duration of use. From observational studies, the risk appeared to return to baseline in about five years after stopping treatment. In addition, observational studies suggest that the risk of breast cancer was greater, and become apparent earlier, with estrogen/progestin combination therapy as compared to estrogen alone therapy.

In the CE/MPA substudy, 26% of the women reported prior use of estrogen alone and/or estrogen/progestin combination hormone therapy. After a mean follow-up of 5.6 years during the clinical trial, the overall relative risk of invasive breast cancer was 1.24 (95% confidence interval 1.01-1.54), and the overall absolute risk was 41 vs. 33 cases per 10,000 women-years, for CE/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 vs. 25 cases per 10,000 women-years, for CE/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 vs. 36 cases per 10,000 women-years for CE/MPA compared with placebo. In the same substudy, invasive breast cancers were larger and diagnosed at a more advanced stage in the CE/MPA 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.

The use of 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.

c. Ovarian cancer.

The CE/MPA substudy of WHI reported that estrogen plus progestin increased the risk of ovarian cancer. After an average follow-up of 5.6 years, the relative risk for ovarian cancer for

CE/MPA versus placebo was 1.58 (95% confidence interval 0.77 – 3.24) but was not statistically significant.

A meta-analysis of 17 prospective and 35 retrospective epidemiology studies found that women who used hormonal therapy for menopausal symptoms had an increased risk for ovarian cancer. The primary analysis, using case-control comparisons, included 12,110 cancer cases from the 17 prospective studies. The relative risks associated with current use of hormonal therapy was 1.41 (95% confidence interval [CI] 1.32 to 1.50); there was no difference in the risk estimates by duration of the exposure (less than 5 years [median of 3 years] vs. greater than 5 years [median of 10 years] of use before the cancer diagnosis). The relative risk associated with combined current and recent use (discontinued use within 5 years before cancer diagnosis) was 1.37 (95% CI 1.27-1.48), and the elevated risk was significant for both estrogen-alone and estrogen plus progestin products. The exact duration of hormone therapy use associated with an increased risk of ovarian cancer, however, is unknown.

3. Dementia.

In the Women's Health Initiative Memory Study (WHIMS), 4,532 generally healthy postmenopausal women 65 years of age and older were studied, of whom 35% were 70 to 74 years of age and 18% were 75 or older. After an average follow-up of 4 years, 40 women being treated with CE/MPA (1.8%, n=2,229) and 21 women in the placebo group (0.9%, n=2,303) received diagnoses of probable dementia. The relative risk for CE/MPA versus placebo was 2.05 (95% confidence interval 1.21 – 3.48), and was similar for women with and without histories of menopausal hormone use before WHIMS. The absolute risk of probable dementia for CE/MPA versus placebo was 45 versus 22 cases per 10,000 women-years, and the absolute excess risk for CE/MPA was 23 cases per 10,000 women-years. It is unknown whether these findings apply to younger postmenopausal women. (See **CLINICAL PHARMACOLOGY, Clinical Studies** and **PRECAUTIONS, Geriatric Use.**)

It is unknown whether these finding apply to estrogen alone therapy.

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. Hypercalcemia.

Estrogen administration may lead to severe hypercalcemia in patients 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.

6. Visual abnormalities.

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

Precautions

A. General

1. *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 a possible increased risk of breast cancer.

2. *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 estrogens on blood pressure was not seen. Blood pressure should be monitored at regular intervals with estrogen use.

3. *Hypertriglyceridemia.*

In patients with pre-existing hypertriglyceridemia, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis and other complications.

4. *Impaired liver function and past history of cholestatic jaundice.*

Estrogens may be poorly metabolized in patients with impaired liver function. For patients 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. *Uterine bleeding.*

Use of PREFEST, can be associated with spotting, uterine bleeding, and anemia.

6. *Hypothyroidism.*

Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Patients with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T4 and T3 serum concentrations in the normal range. Patients dependent on thyroid hormone replacement therapy who are also receiving estrogens may require increased doses of their thyroid replacement therapy. These patients should have their thyroid function monitored in order to maintain their free thyroid hormone levels in an acceptable range.

7. ***Fluid retention.***

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

8. ***Hypocalcemia.***

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

9. ***Exacerbation of endometriosis.***

Endometriosis may be exacerbated with administration of estrogens.

10. ***Exacerbation of other conditions.***

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

B. Patient Information.

Physicians are advised to discuss the contents of the PATIENT INFORMATION leaflet with patients for whom they prescribe PREFEST.

C. Laboratory Tests.

Estrogen administration should be initiated at the lowest dose approved for the indication and then guided by clinical response rather than by serum hormone levels (e.g., estradiol, FSH).

D. Drug/Laboratory Test Interactions.

1. 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.
2. Increased thyroid-binding globulin (TBG) levels leading to increased circulating total thyroid hormone levels as measured by protein-bound iodine (PBI), T₄ levels (by column or by radioimmunoassay) or T₃ levels by radioimmunoassay. T₃ resin uptake is decreased, reflecting the elevated TBG. Free T₄ and free T₃ concentrations are unaltered. Patients on thyroid replacement therapy may require higher doses of thyroid hormone.
3. Other binding proteins may be elevated in serum (i.e., corticosteroid binding globulin (CBG), sex hormone binding globulin (SHBG)) leading to increased total circulating corticosteroids and sex steroids, respectively. Free hormone concentrations may be

decreased. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).

4. Increased plasma HDL and HDL2 cholesterol subfraction concentrations, reduced LDL cholesterol concentration, increased triglycerides levels.
5. Impaired glucose tolerance.
6. Reduced response to metyrapone test.

E. Carcinogenesis, Mutagenesis, and Impairment of Fertility.

Long-term continuous administration of estrogen, with and without progestin, in women with and without a uterus, has shown an increased risk of endometrial cancer, breast cancer, and ovarian cancer. (See **BOXED WARNINGS, WARNINGS** and **PRECAUTIONS**.)

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

F. Pregnancy.

PREFEST should not be used during pregnancy. (See **CONTRAINDICATIONS**.)

G. Nursing Mothers.

Estrogen administration to nursing mothers has been shown to decrease the quantity and quality of the milk. Detectable amounts of estrogens and progestins have been identified in the milk of mothers receiving this drug. Caution should be exercised when PREFEST is administered to a nursing mother.

H. Pediatric Use.

PREFEST is not indicated for use in children.

I. Geriatric Use.

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

In the Women's Health Initiative Memory Study, including 4,532 women 65 years of age and older, followed for an average of 4 years, 82% (n=3,729) were 65 to 74 while 18% (n=803) were 75 and over. Most women (80%) had no prior hormone therapy use. Women treated with conjugated estrogens plus medroxyprogesterone acetate were reported to have a two-fold increase in the risk of developing probable dementia. Alzheimer's disease was the most common classification of probable dementia in both the conjugated estrogens plus medroxyprogesterone acetate group and the placebo group. Ninety percent of the cases of probable dementia occurred in the 54% of women that were older than 70. (See **WARNINGS, Dementia**.)

It is unknown whether these findings apply to estrogen alone therapy.

Adverse Reactions

See **BOXED WARNINGS**, **WARNINGS**, and **PRECAUTIONS**.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials 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. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

Table 7: ALL TREATMENT-EMERGENT ADVERSE EVENTS REGARDLESS OF DRUG RELATIONSHIP REPORTED AT A FREQUENCY OF $\geq 5\%$ WITH PREFEST

FOUR 12-MONTH CLINICAL TRIALS	
	PREFEST (Estradiol and NGM) (N = 579) N (%)
Body as a Whole	
Back pain	69 (12%)
Fatigue	32 (6%)
Influenza-like symptoms	64 (11%)
Pain	37 (6%)
Digestive System	
Abdominal pain	70 (12%)
Flatulence	29 (5%)
Nausea	34 (6%)
Tooth disorder	27 (5%)
Musculoskeletal System	
Arthralgia	51 (9%)
Myalgia	30 (5%)
Nervous System	
Dizziness	27 (5%)
Headache	132 (23%)
Psychiatric Disorders	
Depression	27 (5%)
Reproductive System	
Breast pain	92 (16%)
Dysmenorrhea	48 (8%)

FOUR 12-MONTH CLINICAL TRIALS	
Vaginal bleeding (all)	52 (9%)
Vaginitis	42 (7%)
Resistance Mechanism Disorders	
Viral infection	35 (6%)
Respiratory System	
Coughing	28 (5%)
Pharyngitis	38 (7%)
Sinusitis	44 (8%)
Upper respiratory-tract infection	121 (21%)

The following additional adverse reactions have been reported with estrogen and/or progestin therapy:

1. *Genitourinary system*

Changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow; breakthrough bleeding; spotting; dysmenorrhea, increase in size of uterine leiomyomata; vaginitis, including vaginal candidiasis; change in amount of cervical secretion; changes in cervical ectropion; ovarian cancer; endometrial hyperplasia; endometrial cancer.

2. *Breasts*

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

3. *Cardiovascular*

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

4. *Gastrointestinal*

Nausea, vomiting; abdominal cramps, bloating; cholestatic jaundice; increased incidence of gallbladder disease; pancreatitis, enlargement of hepatic hemangiomas.

5. *Skin*

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

6. *Eyes*

Retinal vascular thrombosis, intolerance to contact lenses.

7. *Central nervous system*

Headache; migraine; dizziness; mental depression; chorea; nervousness; mood disturbances; irritability; exacerbation of epilepsy, dementia.

8. *Miscellaneous*

Increase or decrease in weight; reduced carbohydrate tolerance; aggravation of porphyria; edema; arthralgias; leg cramps; changes in libido; urticaria, angioedema, anaphylactoid/anaphylactic reactions; hypocalcemia; exacerbation of asthma; increased triglycerides.

Overdosage

Serious ill effects have not been reported following acute ingestion of large doses of estrogen-containing drug products by young children. Overdosage of estrogen may cause nausea and vomiting, and withdrawal bleeding may occur in females.

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. Patients should be reevaluated periodically as clinically appropriate (e.g., 3-month to 6-month intervals) to determine if treatment is still necessary (See **BOXED WARNINGS** and **WARNINGS**). For women who have a uterus, adequate diagnostic measures, such as endometrial sampling, when indicated, should be undertaken to rule out malignancy in cases of undiagnosed persistent or recurring abnormal vaginal bleeding.

PREFEST regimen consists of the daily administration of a single tablet containing 1 mg estradiol (pink color) for three days followed by a single tablet of 1 mg estradiol combined with 0.09 mg norgestimate (white color) for three days. This regimen is repeated continuously without interruption.

1. For treatment of moderate to severe vasomotor symptoms and vulvar and vaginal atrophy associated with menopause, the patient should start with the first tablet in the first row, and place the weekday schedule sticker which starts with the weekday of first tablet intake in the appropriate space. After all tablets from the blister card have been used, the first tablet from a new blister card should be taken on the following day.

This dose may not be the lowest effective dose for treatment of vasomotor symptoms and vulvar and vaginal atrophy.

Patients should be re-evaluated at three-month to six-month intervals to determine if treatment for symptoms is still necessary.

2. For prevention of postmenopausal osteoporosis, the patient should start with the first tablet in the first row, and place the weekday schedule sticker which starts with the weekday of first tablet intake in the appropriate space. After all tablets from the blister

card have been used, the first tablet from a new blister card should be taken on the following day.

This dose may not be the lowest effective dose for the prevention of postmenopausal osteoporosis.

Missed Tablets

If a tablet is missed for one or more days, therapy should be resumed with the next available tablet. The patient should continue to take only one tablet each day in sequence.

The lowest effective dose of PREFEST has not been determined.

How Supplied

PREFEST is available as two separate, round-shaped tablets for oral administration supplied in a blister card with the following configuration: 3 pink tablets, followed by 3 white tablets for a total of 30 tablets per blister card.

Each blister card contains 15 tablets of each of the following components:

1 mg estradiol: pink tablets embossed with “1” and “J-C” on one side and “E2” and “O-M” on the other side.

1 mg estradiol/0.09 mg norgestimate: white tablets embossed with “1/90” and “J-C” on one side and “E2/N” and “O-M” on the other side.

NDC: 51285-088-90 PREFEST, 30 Tablets/Blister

This product is stable for 24 months. Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Keep out of reach of children.

Manufactured by:

TEVA WOMEN’S HEALTH, INC.

Subsidiary of TEVA PHARMACEUTICALS USA, INC.

North Wales, PA 19454

Rev. 11/2017

PATIENT INFORMATION

PREFEST

(estradiol/norgestimate)

Read this PATIENT INFORMATION before you start taking PREFEST and read what you get each time you refill PREFEST. 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 PREFEST (a combination of estrogen and progestin hormones)?

·Do not use estrogens and progestins to prevent heart disease, heart attacks, or strokes.

Using estrogens and progestins may increase your chances of getting heart attacks, strokes, breast cancer, and blood clots. Using estrogens with progestins may increase your risk of dementia. You and your healthcare provider should talk regularly about whether you still need treatment with PREFEST.

What Is PREFEST?

PREFEST is a medicine that contains two kinds of hormones, estrogen and a progestin.

What is PREFEST used for?

PREFEST is used after menopause to:

- **reduce moderate or severe hot flashes.**

Estrogens are hormones made by a woman's ovaries. The ovaries normally stop making estrogens when a woman is between 45 to 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 develop 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 estrogens. In other women, symptoms can be more severe. You and your health care provider should talk regularly about whether you still need treatment with PREFEST

- **treat moderate to severe dryness, itching, and burning in and around the vagina.** You and your healthcare provider should talk regularly about whether you still need treatment with PREFEST to control these problems. If you use PREFEST only to treat your dryness, itching, and burning in and around your vagina, talk with your

health care 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 PREFEST only to prevent osteoporosis from menopause, talk with your healthcare provider about whether a different treatment or medicine without estrogens might be better for you. You and your healthcare provider should talk regularly about whether you should continue with PREFEST.

Weight-bearing exercise, like walking or running, and taking calcium and vitamin D 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.

Who Should Not Take PREFEST?

Do not start taking PREFEST if you:

- **have unusual vaginal bleeding.**
- **currently have or have had certain cancers.** Estrogens may increase the chances of getting certain types of cancers, including cancer of the breast or uterus. If you have or had cancer, talk with your healthcare provider about whether you should take PREFEST.
- **had a stroke or heart attack in the past year.**
- **currently have or have had blood clots.**
- **currently have or have had liver problems.**
- **are allergic to PREFEST or any of its ingredients.** See the end of this leaflet for a list of ingredients in PREFEST.
- **think you may be pregnant.**

Tell your healthcare provider:

- **if you are breastfeeding.** The hormones in PREFEST can pass into your milk.
- **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), 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 PREFEST works. PREFEST may also affect how your other medicines work.

- **if you are going to have surgery or will be on bed rest.** You may need to stop taking estrogens.

How Should I Take PREFEST?

- PREFEST therapy consists of taking one single pink tablet (estrogen only) each day for three days followed by one single white tablet (combination of estrogen and progestin) each day for three days. The three days of pink tablets followed by the three days of the white tablets are repeated continuously during treatment.
- If you miss a dose, take it as soon as possible. However, 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 and progestins should be used at the lowest dose possible for your treatment, only as long as needed. The lowest effective dose of PREFEST has not been determined. 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 PREFEST.

What are the possible side effects of estrogens?

Less common but serious side effects include:

- Breast cancer
- Cancer of the uterus
- Stroke
- Heart attack
- Blood clots
- Dementia
- Gallbladder disease
- Ovarian cancer

These are some of the warning signs of serious side effects:

- Breast lumps
- Unusual vaginal bleeding
- Dizziness and faintness
- Changes in speech
- Severe headaches
- Chest pain

- Shortness of breath
- Pains in your legs
- Changes in vision
- Vomiting

Call your healthcare provider right away if you get any of these warning signs, or any other unusual symptom that concerns you.

Common side effects include:

- Headache
- Breast pain
- Irregular vaginal bleeding or spotting
- Stomach/abdominal cramps, bloating
- Nausea and vomiting
- Hair loss

Other side effects include:

- High blood pressure
- Liver problems
- High blood sugar
- Fluid retention
- Enlargement of benign tumors of the uterus (“fibroids”)
- Vaginal yeast infection

These are not all the possible side effects of PREFEST. For more information, ask your healthcare provider or pharmacist.

What can I do to lower my chances of a serious side effect with PREFEST?

Talk with your healthcare provider regularly about whether you should continue taking PREFEST. See your healthcare provider right away if you get vaginal bleeding while taking PREFEST. Have a 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. If you have high blood pressure, high cholesterol (fat in 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 for getting heart disease.

General information about the safe and effective use of PREFEST

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

Keep PREFEST out of reach of children.

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

What are the ingredients in PREFEST?

PREFEST contains two separate tablets. One tablet (pink color) contains 1.0 mg estradiol, croscarmellose sodium, microcrystalline cellulose, magnesium stearate, ferric oxide red, and lactose monohydrate. The other tablet (white color) contains 1.0 mg estradiol, 0.09 mg norgestimate, croscarmellose sodium, microcrystalline cellulose, magnesium stearate, and lactose monohydrate.

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