CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 21040

FINAL PRINTED LABELING

10/22/99 DMI

TEXT OF PROPOSED LABELING: PHYSICIAN'S PACKAGE INSERT

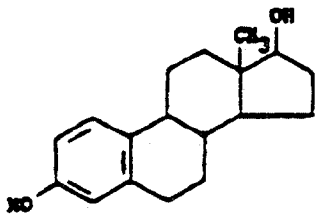
Caution: Federal law prohibits dispensing without a prescription.

ORTHO-PREFEST™ (17β-estradiol/norgestimate) tablets

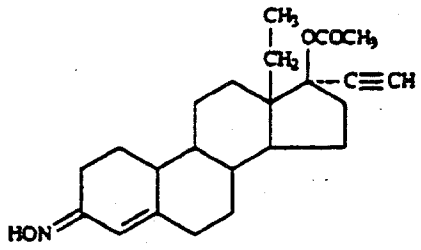
DESCRIPTION

The ORTHO-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 ORTHO-PREFEST™.

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



The progestational component of ORTHO-PREFEST™ is micronized norgestimate, a white powder which is chemically described as (17α)-17-(Acetyloxyl)-13-ethyl-18,19-dinorpregn-4-en-20-yn-3-one3-oxime. 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

Estrogens are important in the development and maintenance of the female reproductive system and secondary sex characteristics. By a direct action, they cause growth and development of the uterus, fallopian tubes, and vagina. With other hormones, such as pituitary hormones and progesterone, they cause enlargement of the breasts through promotion of ductal growth, stromal development, and the accretion of fat. Estrogens are intricately involved with other hormones, especially progesterone, in the processes of the ovulatory menstrual cycle and pregnancy and affect the release of pituitary gonadotropins. They also contribute to the shaping of the skeleton, maintenance of tone and elasticity of urogenital structures, changes in the epiphyses of the long bones that allow for the pubertal growth spurt and its termination, and pigmentation of the nipples and genitals.

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

Circulating estrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone (LH) and follicle stimulating hormone (FSH) through a negative feedback mechanism and estrogen replacement therapy acts 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 ORTHO-PREFEST™ (Table 1). Norgestimate is completely metabolized; it's primary active metabolite, 17-deacetylnorgestimate, reaches C_{max} at approximately 2 hours after dose (Table 1). Upon co-administration of ORTHO-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. Estradiol is bound mainly to sex hormone binding globulin (SHBG), and to 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 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 ORTHO-PREFEST™ is approximately 16 and 37 hours, respectively.

Special Populations

Pediatric: ORTHO-PREFEST™ is not indicated in children.

Geriatric: ORTHO-PREFEST™ has not been studied in geriatric patients

Gender: ORTHO-PREFEST™ is indicated in women only.

Effects of Race, Age, and Body Weight: The effects of race, age, and body weight on the pharmacokinetics of 17β-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 age (40-66 years) was observed. 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.

Renal Insufficiency: It has been reported in the literature that at both baseline and after estradiol ingestion, postmenopausal women with end stage renal disease (ESRD) had higher free serum estradiol levels than the control subjects. No pharmacokinetic study with norgestimate or a hormone combination with norgestimate has been conducted in postmenopausal women with ESRD.

Hepatic Insufficiency: No pharmacokinetic study for ORTHO-PREFEST™ has been conducted in postmenopausal women with hepatic impairment.

Table 1: Mean Pharmacokinetic Parameters of E_2, E_1, E_1S, and 17d-NGM[1] Following Single and Multiple Dosing of ORTHO-PREFEST™

Analyte	Parameter[2]	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_1S	C_{max}	ng/mL	11.1	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[3]	515	NA	643
	t_{max}	h	NA	2	NA	2
	AUC(0-24 h)	pg. h/mL	NA	2146	NA	5322
	t½	h	NA	37	NA	NA

[1] E2 = 17β-Estradiol, E_1 = Estrone, E_1S = Estrone Sulfate, 17d-NGM = 17-deacetylnorgestimate. Baseline uncorrected data are reported for E_2, E_1 and E_1S

[2] Cmax = 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, t½ = half-life

[3] NA= Not available or not applicable

Drug-Drug Interactions

Estradiol, norgestimate, and their metabolites inhibit a variety of P450 enzymes in human liver microsomes. However, the clinical and toxicological consequences of such interaction are likely to be insignificant because, under the recommended dosing regimen, the in vivo concentrations of these steroids, even at the peak serum levels, are relatively low compared to the inhibitory constant (Ki). 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.

CLINICAL STUDIES

Efficacy on Postmenopausal Symptoms

The effect of the estrogen component of ORTHO-PREFEST™ on vasomotor symptoms 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 ORTHO-PREFEST™ regimen) was studied in two 12-month trials in healthy postmenopausal women (n=1212) 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 Moderate-to-Severe Hot Flushes per Day)

	1 mg E2		ORTHO-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-Drug Interactions**).

Efficacy on Vulvar and Vaginal Atrophy

The effect of the estrogen component of ORTHO-PREFEST™ on vulvovaginal 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 ORTHO-PREFEST™ regimen) was studied in a 12-month trial in healthy postmenopausal women 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 ORTHO-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
		ORTHO-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 ORTHO-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	ORTHO-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%)

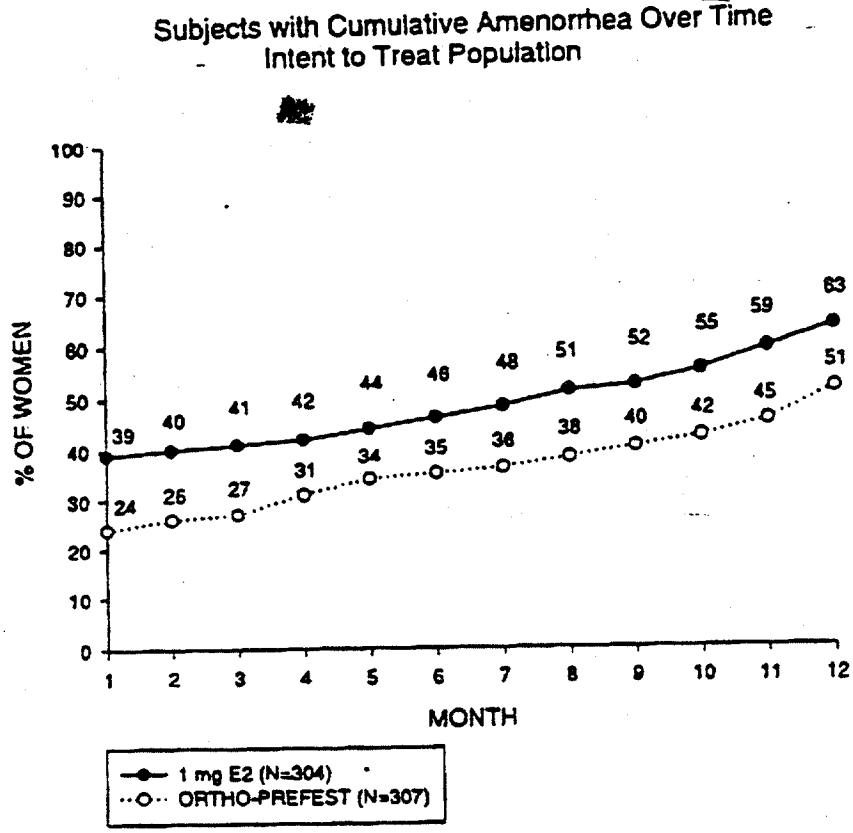
In another 12-month controlled clinical trial for endometrial protection an additional 190 postmenopausal women were treated with ORTHO-PREFEST™. No subject had a diagnosis of endometrial hyperplasia after treatment.

Control of Uterine Bleeding

The effect of ORTHO-PREFEST™ on uterine bleeding was evaluated in two 12-month trials.

Combined results are shown in Figure 1.

Figure 1: Subjects with Cumulative Amenorrhea Over Time (Intent To Treat population)



Note: At each month, the percentage of women who were amenorrheic in that month and through month 12 is shown.

Metabolic Parameters

Effects on Lipids

The effect of ORTHO-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 Blood Lipoproteins at Month 12

	1 mg E_2		ORTHO-PREFEST™	
		Mean %		Mean %
	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

INDICATIONS AND USAGE

ORTHO-PREFEST™ therapy is indicated in women with an intact uterus for the:

1. Treatment of moderate to severe vasomotor symptoms associated with the menopause.

2. Treatment of vulvar and vaginal atrophy.
3. Prevention of osteoporosis.

Most prospective studies of efficacy for this indication have been carried out in white post-menopausal women, without stratification by other risk factors, and tend to show a universally beneficial effect on bone. Since estrogen administration is associated with risk, patient selection must be individualized based on the balance of risks and benefits.

Case-control studies have shown an approximately 60-percent reduction in hip and wrist fractures in women whose estrogen replacement was begun within a few years after menopause. Studies also suggest that estrogen reduces the rate of vertebral fractures. When estrogen therapy is discontinued, bone mass declines at a rate comparable to the immediate postmenopausal period.

White and Asian women are at higher risk for osteoporosis than Black women, and thin women are at higher risk than heavier women, who generally have higher endogenous estrogen levels. Early menopause is one of the strongest predictors for the development of osteoporosis. Other factors associated with osteoporosis include genetic factors (small build, family history), lifestyle (cigarette smoking, alcohol abuse, sedentary exercise habits) and nutrition (below average body weight and dietary calcium intake).

The mainstays of prevention and management of osteoporosis are weight-bearing exercise, adequate lifetime calcium intake, and, when indicated, estrogen. Postmenopausal women absorb dietary calcium less efficiently than premenopausal women and require an average of 1500 mg/day of elemental calcium to remain in neutral calcium balance. The average calcium intake in the USA is 400-600 mg/day. Therefore, when not contraindicated, calcium supplementation may be helpful for women with suboptimal dietary intake.

CONTRAINDICATIONS

Estrogens/progestins should not be used in individuals with any of the following conditions:

1. Known or suspected pregnancy.
2. Undiagnosed abnormal genital bleeding.
3. Known or suspected cancer of the breast.
4. Known or suspected estrogen-dependent neoplasia.
5. Active or past history of thrombophlebitis or thromboembolic disorders.
6. Hypersensitivity to any components of this product.

WARNINGS

Based on experience with estrogens and/or progestins:

1. **Induction of Malignant Neoplasms**

   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 the use of estrogens for less than one year. The greatest risk appears associated with prolonged use, with increased risks of 15 to 24-fold for five years to ten years or more, and this risk has been shown to persist for at least 8-15

years after estrogen therapy is discontinued. Using progestin therapy together with estrogen therapy significantly reduces but does not eliminate this risk.

Results from two 12-month clinical trials of the effects of ORTHO-PREFEST™ on endometrial hyperplasia are shown in the Clinical Studies section of this label.

Appropriate diagnostic measures should be undertaken to rule out malignancy in all cases of undiagnosed, persistent, or recurring abnormal vaginal bleeding.

Breast Cancer

Some studies have reported an increase in the risk of breast cancer in postmenopausal women receiving hormone replacement therapy. A meta-analysis of 51 clinical studies suggests that this increased risk is comparable to that observed in women with every year of delay of natural menopause. This increased risk decreases after cessation of use of hormone replacement therapy and is not apparent five years following cessation of treatment. Breast cancers found in current or recent users of hormone replacement therapy are more likely to be localized to the breast than those in non-users. Concurrent progestin use does not appear to protect against this risk. Therefore, a careful appraisal of the risk/benefit ratio should be undertaken before the initiation of long-term treatment.

Women on hormone replacement therapy should have regular examinations and should be instructed in breast self-examination, and women over the age of 50 should have regular mammograms.

2. **Venous thromboembolism**

Epidemiologic studies have reported an increased risk of venous thromboembolism (VTE) in users of estrogen replacement therapy (ERT) who did not have predisposing conditions for VTE, such as past history of cardiovascular disease or a recent history of pregnancy, surgery, trauma, or serious illness. The increased risk was found only in current ERT users; it did not persist in former users. The findings were similar for ERT alone or with added progestin and pertain to commonly used ERT types and doses, including 0.625 mg or more per day orally of conjugated estrogens, 1 mg or more per day orally of estradiol, and 50 micrograms or more per day or transdermal estradiol. The studies found the VTE risk to be about one case per 10,000 women per year among women not using ERT and without predisposing conditions. The risk in current ERT users was increased to 2-3 cases per 10,000 women per year.

3. **Cardiovascular Disease.**

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

4. **Hypercalcemia.**

Administration of estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases. If this occurs, the drugs should be stopped and appropriate measures taken to reduce the serum calcium level.

5. **Gallbladder Disease.**

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

PRECAUTIONS

General

Based on experience with estrogens and/or progestins:

1. **Addition of a progestin when a women 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.

There are, however, possible risks that may be associated with the use of progestins in estrogen replacement regimens. These include:

a. adverse effects on lipoprotein metabolism (lowering HDL and raising LDL).
b. impairment of glucose tolerance;

and:

c. possible enhancement of mitotic activity in breast epithelial tissue. There is minimal epidemiological data available to address this point.

The choice of progestin, its dose, and its regimen may be important in minimizing these adverse effects.

2. **Elevated blood pressure**

Occasional increases in blood pressure during estrogen replacement therapy have been attributed to idiosyncratic reactions to estrogens in a small number of case reports. A generalized effect of estrogen therapy on blood pressure was not found in the one randomized, placebo-controlled study that has been reported. This effect was also not observed in clinical studies with ORTHO-PREFEST™.

3. **Familial hyperlipoproteinemia**

Estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis and other complications in patients with familial defects of lipoprotein metabolism.

4. **Impaired liver function.**

Estrogens may be poorly metabolized in patients with impaired liver function.

Information For The Patient

See text of PATIENT LABELING, below.

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 anti-factor 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) leading to increased circulating total thyroid hormone, 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.
3. Other binding proteins may be elevated in serum, i.e., corticosteroid binding globulin (CBG), sex hormone-binding globulin (SHBG), leading to increased circulating corticosteroids and sex steroids respectively. Free or biologically active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).
4. Increased plasma HDL and HDL-2 subfraction concentrations, reduced LDL cholesterol concentration, increased triglycerides levels.
5. Impaired glucose tolerance. For this reason, diabetic patients should be carefully observed while receiving estrogen/progestin therapy.
6. Reduced response to metyrapone test.
7. Reduced serum folate concentration.

Carcinogenesis, Mutagenesis, And 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. (See **CONTRAINDICATIONS** and **WARNINGS**.)

Pregnancy Category X

ORTHO-PREFEST™ should not be used during pregnancy. [See **CONTRAINDICATIONS**.]

Nursing Mothers

As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk. Estrogen administration to nursing mothers has been shown to decrease the quantity and quality of the milk. Estrogens are not indicated for the prevention of postpartum breast engorgement.

ADVERSE REACTIONS

In four 12-month trials that included 579 healthy postmenopausal women treated with ORTHO-PREFEST™ the following treatment-emergent adverse events occurred at a rate ≥5% (Table 6):

Table 6: All Treatment-Emergent Adverse Events Regardless Of Drug Relationship Reported At A Frequency Of ≥ 5% With ORTHO-PREFEST™

Four 12-Month Clinical Trials	ORTHO-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%)
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 therapy (see **WARNINGS** and **PRECAUTIONS** regarding induction of neoplasia, increased incidence of gallbladder disease, cardiovascular disease, elevated blood pressure, and hypercalcemia).

1. **Genitourinary System.** Changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow; breakthrough bleeding, spotting; increase in size of uterine leiomyomata; vaginal candidiasis; change in amount of cervical secretion.

2. **Breasts.** Tenderness, enlargement, galactorrhea.

3. **Gastrointestinal.** Cholestatic jaundice, nausea, vomiting; abdominal cramps, bloating, increased incidence of gall bladder disease.

4. **Skin.** Chloasma or melasma; which may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair; hirsutism.

5. **Central Nervous System.** Headache, migraine, dizziness; mental depression; chorea.

6. **Eyes.** Steepening of corneal curvature; intolerance to contact lenses.

7. **Miscellaneous.** Increase or decrease in weight; reduced carbohydrate tolerance; aggravation of porphyria; edema; changes in libido.

OVERDOSAGE

No serious ill effects have been reported following acute ingestion of large doses of estrogen/ progestin -containing oral contraceptives by young children. Overdosage may cause nausea and vomiting, and withdrawal bleeding may occur in females.

DOSAGE AND ADMINISTRATION

ORTHO-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 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 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 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.

HOW SUPPLIED:

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

NDC: 0062-1840-01 ORTHO-PREFEST™, 30 Tablets/Blister

This product is stable for 18 months. Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F).