

# **PRODUCT MONOGRAPH**

**FEMHRT**  
**(Norethindrone Acetate [NA] and Ethinyl Estradiol [EE])**

**0.5 mg NA and 2.5  $\mu$ g EE Tablets**  
**1 mg NA and 5  $\mu$ g EE Tablets**

**Estrogen-Progestin Combination**

Warner Chilcott Company, LLC.  
Union Street, Road 195, Km 1.1  
Fajardo, Puerto Rico 00738

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**femHRT<sup>®</sup>**

**(Norethindrone Acetate [NA] and Ethinyl Estradiol [EE] Tablets)**

0.5 mg NA and 2.5 µg EE  
1 mg NA and 5 µg EE

**PART I: HEALTH PROFESSIONAL INFORMATION**

**INDICATIONS AND CLINICAL USE**

femHRT tablets are a combination of ethinyl estradiol (estrogen) and norethindrone acetate (progestin) intended for continuous administration as hormone replacement therapy.

femHRT is indicated for:

- Relief of menopausal and postmenopausal symptoms occurring in naturally or surgically induced estrogen deficiency states;
- Symptomatic treatment of vulvar and vaginal atrophy associated with menopause;
- Prevention of osteoporosis in naturally occurring or surgically induced estrogen-deficiency states in addition to other important therapeutic measures such as sufficient calcium and vitamin D intake, cessation of smoking and regular physical weight bearing exercise. 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.

**femHRT<sup>®</sup> is recommended for use only in patients with an intact uterus, since the regimen includes a progestin whose role is to prevent endometrial hyperplasia.**

Estrogen replacement therapy reduces bone resorption and retards or halts postmenopausal loss. When estrogen therapy is discontinued, bone mass declines at a rate comparable to that in the immediate postmenopausal period. There is no evidence that estrogen replacement therapy restores bone mass to premenopausal levels.

At skeletal maturity there are sex and race differences in both the total amount of bone present and its density, in favour of men. Thus, women are at higher risk than men because they start with less bone mass and, for several years following natural or induced menopause, the rate of bone mass decline is accelerated. White and Asian women are also at higher risk than black women.

Early menopause is one of the strongest predictors for development of osteoporosis. In addition, other factors affecting the skeleton, which are associated with osteoporosis, include genetic factors (small build, family history), endocrine factors (nulliparity, thyrotoxicosis, hyperparathyroidism, Cushing's syndrome, hyperprolactinemia, type I

diabetes), lifestyle (cigarette smoking, alcohol abuse, sedentary lifestyles), and nutrition (below average body weight, low dietary calcium intake).

The mainstays for decreasing the risk of osteoporosis are an adequate calcium and vitamin D intake, weight bearing exercise, smoking cessation and when indicated, pharmacologic measures. 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. By comparison, premenopausal women require about 1000 mg/day, and the average calcium intake in North America is 400-600 mg/day. Therefore, when not contraindicated, calcium supplementation may be helpful. Vitamin D supplementation of 400-800 IU/day may also be required to ensure adequate daily intake in postmenopausal women.

Weight bearing exercise and nutrition are important in the prevention and management of osteoporosis. Immobilization and prolonged bed rest produce rapid bone loss, while weight-bearing exercise has been shown to reduce bone loss and increase bone mass. The optimal types and amount of physical activity that would prevent osteoporosis have not been established; however, in two studies, an hour of walking and running exercises two or three times weekly significantly increased lumbar spine bone mass.

## **CONTRAINDICATIONS**

femHRT (norethindrone acetate and ethinyl estradiol) is contraindicated in patients with any of the following disorders:

- Active hepatic dysfunction or disease, especially of the obstructive type
- Personal history of known or suspected estrogen/progestin-dependent neoplasia, such as breast or endometrial cancer
- Endometrial hyperplasia
- Undiagnosed abnormal genital bleeding
- Known or suspected pregnancy
- Lactation
- Active or past history of arterial thromboembolic disease (e.g., stroke, myocardial infarction, coronary heart disease)
- Classical migraine
- Active or past history of confirmed venous thromboembolism (such as deep venous thrombosis or pulmonary embolism) or active thrombophlebitis
- Partial or complete loss of vision due to ophthalmic disease
- Known or suspected hypersensitivity to any components of the medication

## WARNINGS AND PRECAUTIONS

### SERIOUS WARNINGS AND PRECAUTIONS

As the Women's Health Initiative (WHI) study results indicated increased risk of myocardial infarction (MI), stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women during 5 years of treatment with combined 0.625 mg conjugated equine estrogens and 2.5 mg medroxyprogesterone acetate compared to those receiving placebo tablets, the following should be highly considered:

- Estrogens with or without progestins **should not** be prescribed for primary or secondary prevention of cardiovascular diseases.
- Other combinations of estrogens and progestins were not studied in the WHI 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** possible for the recognized indication.
- 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.

### General

Before femHRT (norethindrone acetate and ethinyl estradiol) is administered, the patient should have a complete physical examination including a blood pressure determination. Breasts and pelvic organs should be appropriately examined and a Papanicolaou smear should be performed. Endometrial thickness should be evaluated by ultrasound and/or by endometrial biopsy, when indicated. Baseline tests should include mammography, measurements of blood glucose, calcium, triglycerides and cholesterol, and liver function tests.

The first follow-up examination should be done within 3-6 months after initiation of treatment to assess response to treatment. Thereafter, examinations should be made every 6-12 months and should include at least those procedures outlined above.

**It is important that patients are encouraged to practice frequent self-examination of the breasts.**

### Carcinogenesis and Mutagenesis

#### **Breast Cancer**

Current epidemiological data indicate that the use of combined HRT is associated with an increased risk of invasive breast cancer. The WHI trial results concluded that there are more risks than benefits among women using combined HRT (0.625 mg conjugated equine estrogens/2.5 mg medroxyprogesterone acetate) compared to the group using

placebo. In 10,000 women on combined HRT over one year period, there were eight more cases of invasive breast cancer (38 on combined HRT versus 30 on placebo per 10,000 person-years).

The WHI study reported that the invasive breast cancers diagnosed in the estrogen plus progestin group were similar in histology but were larger (mean [SD], 1.7 cm [1.1] vs. 1.5 cm [0.9], respectively;  $P=0.04$ ) and were at a more advanced stage compared with those diagnosed in the placebo group.

The WHI trial also reported that the percentage of women with abnormal mammograms (recommendations for short-interval follow-up, a suspicious abnormality, or highly suggestive of malignancy) was significantly higher in the estrogen plus progestin group versus the placebo group. This difference appeared at year one and persisted in each year thereafter.

Two breast neoplastic events occurred across the four pivotal femHRT trials described in the Clinical Trials section. Both events occurred in Study 376-359: One breast cancer occurred on Day 164 in a subject randomized to 0.5/2.5 (n=136) dose. Tumor marker studies were negative for estrogen and progesterone receptors. A recurrence of cancer was reported on follow-up. One breast cancer occurred at an unknown onset date in a subject randomized to the 1/5 dose (n=146). Drug was permanently discontinued. On follow-up, drug-related causality could not be ruled out.

It is recommended that estrogens not be given to women with existing breast cancer or those with a previous history of the disease. There is a need for caution in prescribing estrogens for women with known risk factors associated with the development of breast cancer, such as strong family history of breast cancer (first degree relative) or who present a breast condition with an increased risk (abnormal mammograms and/or atypical hyperplasia at breast biopsy). Other known risk factors for the development of breast cancer such as nulliparity, obesity, early menarche, late age at first full term pregnancy and at menopause should also be evaluated.

It is recommended that women undergo mammography before starting HRT, and at regular intervals during treatment, as deemed appropriate by the treating physician and according to the perceived risks for each patient.

The overall benefits and possible risks of hormone replacement therapy should be fully considered and discussed with patients. It is important that the modest increase in risk of being diagnosed with breast cancer after 4 years of treatment with HRT (as reported in the results of the WHI trial) be discussed with the patient and weighed against its known benefits.

**Instructions for regular self-examination should be included in this counselling.**

## **Endometrial Hyperplasia and Endometrial Carcinoma**

There is evidence from several studies that estrogens unopposed by progestins increase the risk of carcinoma of the endometrium in humans. femHRT (norethindrone acetate and ethinyl estradiol) provides plasma norethindrone levels within the appropriate range to counteract the effects of ethinyl estradiol on the endometrium.

In the CHART *Study* (376-359) (See CLINICAL TRIALS), it has been demonstrated that when norethindrone acetate is administered with ethinyl estradiol, the incidence of endometrial hyperplasia (a possible precursor of endometrial cancer) is reduced to the level observed in placebo users. No cases of endometrial hyperplasia were detected with femHRT 0.5/2.5 and 1/5 doses administered for 2 years. femHRT 0.5/2.5 and 1/5 treatment groups did not differ from placebo with regard to the degree of endometrial proliferation.

*Study 376-401* (see CLINICAL TRIALS) assessed the safety and endometrial protective effect of femHRT 1/5 in healthy, postmenopausal women. At the end of 1 year, there were no cases of endometrial hyperplasia reported with femHRT 1/5.

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.

## **Cardiovascular**

Available epidemiological data indicate that use of estrogen with or without progestin is associated with an increased risk of stroke and coronary heart disease. The WHI trial results concluded that there are more risks than benefits among women using combined Hormone Replacement Therapy (HRT), consisting of 0.625 mg conjugated equine estrogens plus 2.5 mg medroxyprogesterone acetate, compared to the group using placebo. In 10,000 women on this combined HRT over one year period, there were seven more cases of coronary heart disease (37 on combined HRT versus 30 on placebo per 10,000 person years) and eight more cases of strokes (29 versus 21 per 10,000 person years).

No cardiovascular event occurred in the femHRT clinical trials described in the Clinical Trials section using the recommended therapeutic doses of femHRT.

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

heart disease. There were more CHD events in the hormone-treated group than in the placebo group in year 1, but not during the subsequent years.

From the original HERS trial, 2321 women consented 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. After 6.8 years, hormone therapy did not reduce the risk of cardiovascular events in women with CHD.

In *Study 376-359*, one transient ischemic attack was reported on Day 611 in a subject randomized to the femHRT 0.5/2.5 dose (n=136). The patient recovered from the upper extremity numbness, and medication was discontinued at study completion on Day 730.

### **Venous Thromboembolism**

Recent epidemiological data indicate that the use of estrogen with or without progestin is associated with an increased risk of developing venous thromboembolism (VTE). The WHI trial results concluded that there are more risks than benefits among women using combined HRT (0.625 mg conjugated equine estrogens/2.5 mg medroxyprogesterone acetate), compared to the group using placebo. In 10,000 women on combined HRT over a period of one year, there were eighteen more cases of total blood clots in the lungs and legs (34 on combined HRT versus 16 on placebo per 10,000 person-years).

One venous thromboembolic event occurred across the four pivotal femHRT trials described in the Clinical Trials section. One deep venous thrombosis was reported on Day 588 of Study 376-359 in a subject randomized to the femHRT 1/5 dose (n=146). Study medication was discontinued, and the subject was hospitalized for anticoagulant therapy. Diagnosis upon hospital discharge was resolving deep vein thrombosis.

Generally recognized risk factors for VTE include a personal history, a family history (the occurrence of VTE in a direct relative at a relatively early age may indicate genetic predisposition) and severe obesity (body mass index  $>30 \text{ kg/m}^2$ ). The risk of VTE also increases with age and smoking.

The risk of VTE may be temporarily increased with prolonged immobilization, major elective surgery or post-traumatic surgery, or major trauma. If feasible, hormone replacement therapy should be discontinued at least 4 weeks before major surgery or during periods of prolonged immobilization, since these events may be associated with an increased risk of thromboembolism. In women on HRT, attention should be given to prophylactic measures to prevent VTE following surgery. In women on HRT, attention should be given to prophylactic measures to prevent VTE following surgery. Also, patients with varicose veins should be closely supervised.

The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, retinal thrombosis, cerebral embolism and pulmonary embolism). If these occur or are suspected, femHRT therapy should be discontinued immediately.

## **Blood Pressure**

Women using hormone replacement therapy sometimes experience increased blood pressure, which, in most cases, returns to normal upon discontinuing the drug. Blood pressure should be monitored with HRT use. Elevation of blood pressure in previously normotensive or hypertensive patients should be evaluated, and femHRT therapy may have to be discontinued.

## **Endocrine and Metabolism**

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

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

Women with familial hypertriglyceridemia or porphyria need special surveillance. Lipid lowering measures are recommended before starting treatment in these women.

## **Genitourinary**

Abnormal vaginal bleeding that is prolonged, irregular or heavy, occurring during therapy should prompt diagnostic measures like endometrial biopsy or dilation and curettage (D & C) to rule out the possibility of uterine malignancy, and the treatment should be re-evaluated.

Pre-existing uterine leiomyoma may increase in size during estrogen use. This is usually minimal, especially in patients who are well past the menopause. Growth, pain or tenderness of uterine leiomyoma requires prompt attention and, if necessary, discontinuation of medication.

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

## **Hematologic**

If feasible, hormone replacement therapy should be discontinued at least 4 weeks before major surgery or during periods of prolonged immobilization, since these events may be associated with an increased risk of thromboembolism.

### **Hepatic/Biliary/Pancreatic**

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

Caution is advised in patients with a history of estrogen-related jaundice and pruritis. If cholestatic jaundice develops during treatment with femHRT, the drug should be discontinued and appropriate investigations carried out.

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

The effect of hepatic disease on the disposition of femHRT has not been evaluated. However, ethinyl estradiol and norethindrone may be poorly metabolized in patients with impaired liver function (see CONTRAINDICATIONS).

### **Neurologic**

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

### **Renal**

Estrogens may cause fluid retention. Therefore, particular attention is indicated in cardiac or renal dysfunction, epilepsy or asthma. Treatment should be stopped if there is an increase in epileptic seizures. If, in any of the above-mentioned conditions, a worsening of the underlying disease is diagnosed or suspected during treatment, the benefits and risks of treatment should be reassessed based on the individual case.

The effect of renal disease on the disposition of femHRT has not been evaluated. In premenopausal women with chronic renal failure undergoing peritoneal dialysis who received multiple doses of an oral contraceptive containing ethinyl estradiol and norethindrone, plasma ethinyl estradiol concentrations were higher and norethindrone concentrations were unchanged compared to concentrations in premenopausal women with normal renal function.

### **Special Populations**

#### **Pregnant Women:**

Estrogens/progestins should not be used during pregnancy (see CONTRAINDICATIONS).

#### **Geriatrics (≥ 65 years of age):**

Current epidemiological evidence suggests that the use of combined HRT is associated with an increased risk of developing dementia. The Women's Health Initiative Memory Study, a clinical sub study of the WHI, followed 4532 post-menopausal women age 65 and over and free of dementia at baseline. There was a reported two-fold increase in the relative risk of developing probable dementia after an average follow-up of 4.05 years in the group treated with daily 0.625 mg conjugated equine estrogen plus 2.5 mg medroxyprogesterone versus those treated with placebo (hazard ratio [HR] 2.05, 95% confidence interval [CI], 1.21-3.480. This increased risk would result in an additional 23 cases of dementia per 10,000 women per year (45 vs. 22 per 10,000 person-years; P=0.01).

The pharmacokinetics of norethindrone acetate and ethinyl estradiol was not affected by age (age range 40-62), in the postmenopausal population studied.

### **Monitoring and Laboratory Tests**

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

- Increased sulfobromophthalein retention
- Increased prothrombin time and partial thromboplastin time; increased levels of fibrinogen and fibrinogen activity; increased coagulation factors VII, VIII, IX, and X; increased norepinephrine-induced platelet aggregability; decreased antithrombin III
- Increased thyroxin-binding globulin (TBG), leading to increased circulating total thyroid hormone (T4) as measured by column or radioimmunoassay; free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered
- Other binding proteins may be elevated in serum, i.e., corticosteroid binding globulin (CBG), sex-hormone binding globulin (SHBG), leading to increased circulating corticosteroids and sex steroids respectively; free or biologically active hormone concentrations are unchanged
- Impaired glucose tolerance
- Reduced response to the METOPIRONE<sup>®</sup> test
- Reduced serum folate concentration
- Increased serum triglyceride and phospholipid concentration

The results of the above laboratory tests should not be considered reliable unless therapy has been discontinued for 2 to 4 weeks. The pathologist should be informed that the patient is receiving estrogen-progestin therapy when relevant specimens are submitted.

### **ADVERSE REACTIONS**

Adverse events reported in placebo controlled clinical studies of femHRT at a frequency of  $\geq 5\%$  are shown in Table 1 below.

**TABLE 1. All Treatment-Emergent Adverse Events Reported at a Frequency of  $\geq 5\%$  of Patients with femHRT**

BODY SYSTEM/ Adverse Event	Percent of Patients (%)		
	Placebo	femHRT 0.5/2.5	femHRT 1/5
	N = 247	N = 244	N = 258
<b>BODY AS A WHOLE</b>	<b>40.1</b>	<b>38.5</b>	<b>39.5</b>
Headache	14.6	15.2	18.2
Back Pain	5.3	5.3	4.7
Viral Infection	7.7	8.6	7.0
<b>DIGESTIVE SYSTEM</b>	<b>24.4</b>	<b>30.5</b>	<b>33.0</b>
Nausea and/or Vomiting	5.3	5.3	7.4
Abdominal Pain	4.5	10.2	8.1
Dyspepsia	2.0	5.3	3.1
Diarrhea	3.6	5.7	3.9
<b>MUSCULOSKELETAL SYSTEM</b>	<b>21.7</b>	<b>20.3</b>	<b>20.4</b>
Arthralgia	6.9	2.9	5.8
Myalgia	8.5	8.6	7.8
<b>PSYCHOBIOLOGIC FUNCTION</b>	<b>8.3</b>	<b>7.9</b>	<b>14.1</b>
Nervousness	1.6	1.6	5.4
Depression	3.6	3.7	5.8
<b>RESPIRATORY SYSTEM</b>	<b>37.2</b>	<b>33.9</b>	<b>35.6</b>
Rhinitis	15.4	12.7	15.1
Sinusitis	9.7	9.4	8.1
<b>UROGENITAL SYSTEM</b>	<b>25.0</b>	<b>31.6</b>	<b>40.8</b>
Breast Pain	5.3	9.0	8.1
Urinary Tract Infection	3.2	3.7	6.2
Vaginitis	4.9	4.5	5.4

**Post-Market Adverse Drug Reactions**

The following adverse reactions have been reported with estrogens/progestin combinations in general:

- **Gastrointestinal:** nausea, vomiting, abdominal discomfort (cramps, pressure, pain), bloating, gallbladder disorder, asymptomatic impaired liver function, cholestatic jaundice

- **Genitourinary:** breakthrough bleeding, spotting, change in menstrual flow, dysmenorrhea, vaginal itching/discharge, dyspareunia, endometrial hyperplasia, premenstrual-like syndrome, reactivation of endometriosis, cystitis, changes in cervical erosion and amount of cervical secretion
- **Skin:** chloasma or melasma, which may persist when drug is discontinued, erythema multiforme, erythema nodosum, hemorrhagic eruption, loss of scalp hair, hirsutism, acne
- **Endocrine:** breast swelling and tenderness, increased blood sugar levels, decreased glucose tolerance, sodium retention
- **Cardiovascular/Hematologic:** palpitations, isolated cases of thrombophlebitis, thromboembolic disorder, exacerbation of varicose veins, increase in blood pressure (see Warnings and Precautions), coronary thrombosis, altered coagulation tests, (see Monitoring and Laboratory Tests under Warnings and Precautions)
- **Central Nervous System:** aggravation of migraine episodes, headaches, mental depression, nervousness, dizziness, fatigue, irritability, neuro-ocular lesions (e.g., retinal thrombosis, optic neuritis).
- **Ophthalmic:** visual disturbances, steepening of the corneal curvature, intolerance to contact lenses, (see CNS, above)
- **Miscellaneous:** changes in appetite, changes in body weight, edema, neuritis, change in libido; musculoskeletal pain, including leg pain not related to thromboembolic disease (usually transient, lasting 3-6 weeks), may occur

**If adverse symptoms persist, the prescription of hormone replacement therapy should be re-evaluated.**

## **DRUG INTERACTIONS**

### **Overview**

No drug-drug interaction studies have been conducted with femHRT. The following section contains information on drug interactions with ethinyl estradiol-containing products (specifically, oral contraceptives) that have been reported in the published literature. It is unknown whether such interactions occur with femHRT or drug products containing other types of estrogens.

### **Drug-Drug Interactions**

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

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

- The metabolism of ethinyl estradiol is increased by rifampin and anticonvulsants such as phenobarbital, phenytoin and carbamazepine. Coadministration of troglitazone and certain ethinyl estradiol-containing drug products (e.g., oral contraceptives containing ethinyl estradiol) reduce the plasma concentration of ethinyl estradiol by 30 percent.

Ascorbic acid and acetaminophen (gram doses) may increase AUC and/or plasma concentration of ethinyl estradiol. Coadministration of atorvastatin and ethinyl estradiol-containing oral contraceptives increased AUC values for ethinyl estradiol by 20%.

Clinical pharmacokinetic studies have not demonstrated any consistent effect of antibiotics (other than rifampin) on plasma concentrations of synthetic steroids.

- Drug products containing ethinyl estradiol may inhibit the metabolism of other compounds. Increased plasma concentrations of cyclosporine, prednisolone and theophylline have been reported with concomitant administration of oral contraceptives containing ethinyl estradiol. In addition, these drugs containing ethinyl estradiol may induce the conjugation of other compounds.

Decreased plasma concentrations of acetaminophen and increased clearance of temazepam, salicylic acid, morphine and clofibric acid have been noted when these drugs were administered with certain ethinyl estradiol-containing drug products (e.g., oral contraceptive containing ethinyl estradiol).

### **Drug-Food Interactions**

femHRT may be taken without regard to meals.

### **Drug-Herb Interactions**

It was found that some herbal products (e.g., St. John's Wort), which are available as OTC products might affect metabolism, and therefore, efficacy and safety of estrogen/progestin combination products.

Physicians and other healthcare providers should be aware of other non-prescription products concomitantly used by the patient, including "herbal" and "natural" products made widely available through Health Food and pharmacy outlets.

## **DOSAGE AND ADMINISTRATION**

### **Dosing Considerations**

Treated patients with an intact uterus should be monitored closely for signs of endometrial cancer, and appropriate diagnostic measures should be taken to rule out malignancy in the event of persistent or recurring vaginal bleeding. Patients should be evaluated at least annually for breast abnormalities and more often, if there are any symptoms.

### **Recommended Dose and Dosage Adjustment**

femHRT (norethindrone acetate and ethinyl estradiol) therapy consists of a single tablet to be taken once daily, without regard for meals.

#### **1. Treatment of Vasomotor Symptoms**

femHRT 0.5/2.5 or 1/5 should be given once daily for the treatment of moderate to severe vasomotor symptoms associated with the menopause. Patients should be re-evaluated within 3-6 months after initiation of treatment, to assess response to treatment.

#### **2. Symptomatic Treatment of Vulvar and Vaginal Atrophy Associated with Menopause**

femHRT 0.5/2.5 or 1/5 should be given once daily for the treatment of vulvar and vaginal atrophy associated with the menopause. Patients should be re-evaluated within 3-6 months after initiation of treatment, to assess response to treatment.

#### **3. Prevention of Osteoporosis**

femHRT 0.5/2.5 or 1/5 should be given once daily to prevent postmenopausal osteoporosis (see CLINICAL TRIALS: Effect on Bone Mineral Density). Response to therapy can be assessed by measurement of bone mineral density.

### **Missed Dose**

If the patient forgets to take the pill at the usual time, it should be taken as soon as she remembers. If it is almost time for the next pill, the missed dose should be skipped and the next pill in the pack should be taken. Two pills should not be taken at once.

### **OVERDOSAGE**

**Symptoms:** Numerous reports of ingestion of large doses of estrogen products and estrogen-containing oral contraceptives by young children have not revealed acute serious ill effects. Overdosage with estrogen may cause nausea, breast discomfort, fluid retention, bloating or vaginal bleeding in women.

Progestin (norethindrone acetate) overdosage has been characterized by depressed mood, tiredness, acne and hirsutism.

**Treatment:** In case of overdose or accidental ingestion by children, the physician should observe the patient closely and provide symptomatic treatment. Gastric lavage should be given if considered necessary.

## **ACTIONS AND CLINICAL PHARMACOLOGY**

### **Mechanism of Action**

femHRT (norethindrone acetate and ethinyl estradiol, NA/EE) is a continuous dosage regimen of an estrogen-progestin combination for oral administration as hormone replacement therapy (HRT). femHRT manages hypoestrogenic states, especially those associated with menopause, and following oophrectomy.

Estrogen drug products, including ethinyl estradiol, act by regulating the transcription of a limited number of genes. Estrogens diffuse through cell membranes, distribute themselves throughout the cell, and bind to and activate the nuclear estrogen receptor, a DNA-binding protein, which is found in estrogen-responsive tissues. The activated estrogen receptor binds to specific DNA sequences, or hormone-response elements, which enhance the transcription of adjacent genes and in turn lead to the observed effects. Estrogen receptors have been identified in tissues of the reproductive tract, breast, pituitary, hypothalamus, liver, arterial wall and bone of women.

Progestins, including norethindrone, exert their effects in target cells by binding to specific progesterone receptors that interact with progesterone response elements in target genes. Progesterone receptors have been identified in the female reproductive tract, breast, pituitary, hypothalamus, bone, skeletal tissue and central nervous system. Norethindrone produces similar endometrial changes to those of naturally occurring hormone progesterone.

### **Pharmacodynamics**

#### **Estrogens**

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 interconversion, 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 µg 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. The pharmacologic effects of ethinyl estradiol are similar to those of endogenous estrogens.

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

Estrogen replacement therapy decreases the rate of bone loss in menopausal women; evidence of estrogen receptors on bone cells suggests there is a direct effect of estrogen on bone. Estrogens also have direct effects on arterial walls through genomic and non-genomic effects.

### Progestin

It has been established that the inclusion of either cyclic or continuous progestin, including norethindrone acetate, in hormone replacement therapy inhibits endometrial proliferation induced by estrogen. The inhibition of endometrial proliferation is associated with a reduction in risk of endometrial hyperplasia and the attendant risk of carcinoma in women with intact uteri.

Progestin compounds enhance cellular differentiation and generally oppose the actions of estrogens by decreasing estrogen receptor levels, increasing local metabolism of estrogens to less active metabolites, or inducing gene products that blunt cellular responses to estrogen.

### Pharmacokinetics

#### **Absorption**

Norethindrone acetate (NA) and ethinyl estradiol (EE) are rapidly absorbed from femHRT tablets, with maximum plasma concentrations of norethindrone and ethinyl estradiol generally occurring 1 to 2 hours postdose. Both are subject to first-pass metabolism after oral dosing, resulting in a bioavailability of approximately 64% for norethindrone and 55% for ethinyl estradiol. Bioavailability of femHRT tablets is similar to that from solution for norethindrone and slightly less for ethinyl estradiol absorption. Administration of femHRT with a high fat meal decreases rate but not extent of ethinyl estradiol absorption. The extent of norethindrone absorption is increased by 27% following administration with food.

The full pharmacokinetic profile of femHRT (0.5 mg NA/2.5 µg EE and 1 mg NA/5 µg EE) was not characterized due to assay sensitivity limitations. Multiple-dose pharmacokinetics of 1 mg NA/10 µg EE tablets were studied in 18 postmenopausal women. Mean plasma concentrations of norethindrone and ethinyl estradiol are shown in Figure 1 and pharmacokinetic parameters are found in Table 2 below. Based on a population pharmacokinetic analysis, mean steady-state concentrations of norethindrone

for the 1 mg NA/5 µg EE (1/5) and 1 mg NA/10 µg EE (1/10) tablets are slightly more than proportional to dose when compared to the 0.5 mg NA/ 2.5 µg EE (0.5/2.5) tablet, which is largely explained by higher sex hormone binding globulin (SHBG) concentrations. Mean steady-state plasma concentrations of ethinyl estradiol for the femHRT 0.5/2.5 and femHRT 1/5 tablets are proportional to dose, but there is a less than proportional increase in steady state concentration for the NA/EE 1/10 tablet.

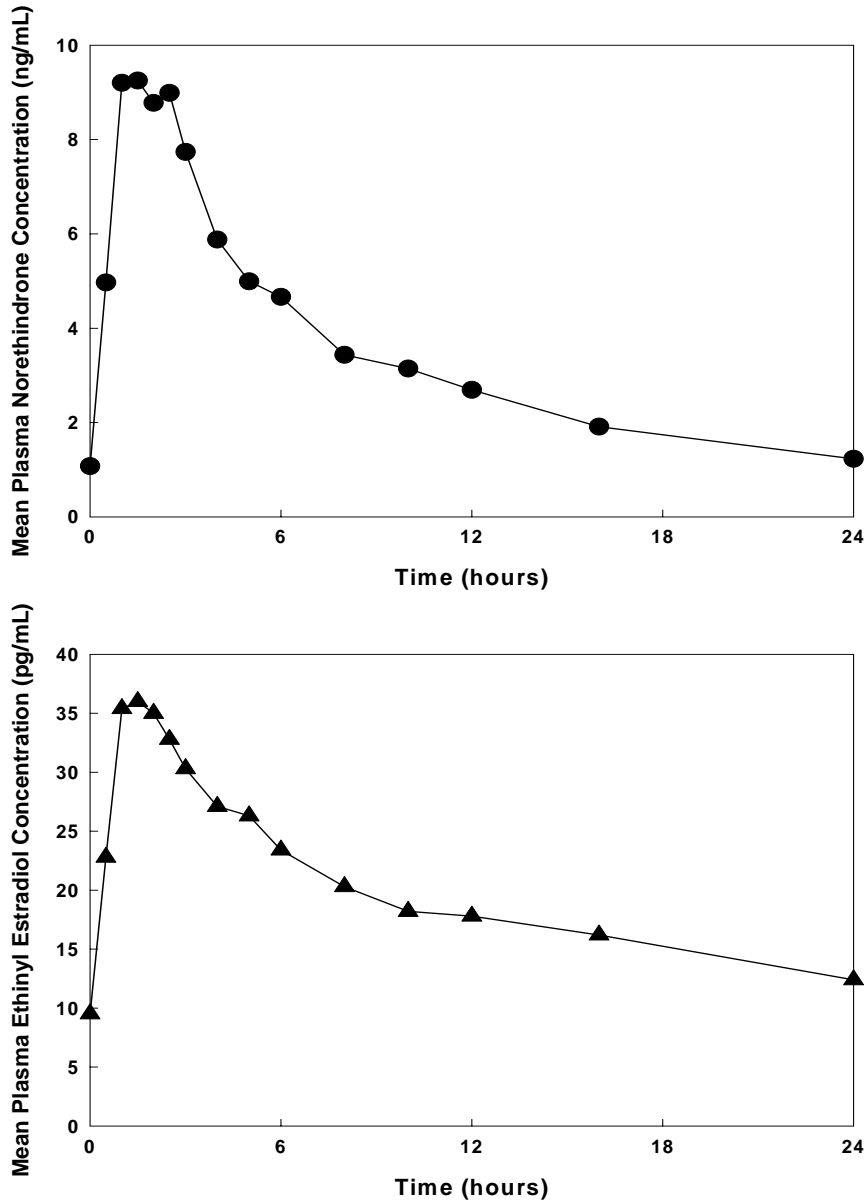


FIGURE 1. Mean Steady-State (Day 87) Plasma Norethindrone and Ethinyl Estradiol Concentrations Following Chronic Administration of NA 1mg/EE 10 µg Tablets.

**Table 2. Mean (SD) Single-Dose (Day 1) and Steady-State (Day 87) Pharmacokinetic Parameters<sup>a</sup> Following Administration of 1 mg NA/10 µg EE Tablets**

	$C_{max}$	$t_{max}$	AUC (0-24)	CL/F	$t_{1/2}$
Norethindrone	ng/mL	hr	ng.hr/mL	mL/min	hr
Day 1	6.0 (3.3)	1.8 (0.8)	29.7 (16.5)	588 (416)	10.3 (3.7)
Day 87	10.7 (3.6)	1.8 (0.8)	81.8 (36.7)	226 (139)	13.3 (4.5)

Ethinyl Estradiol	pg/mL	hr	pg.hr/mL	mL/min	hr
Day 1	33.5 (13.7)	2.2 (1.0)	339 (113)	ND <sup>b</sup>	ND <sup>b</sup>
Day 87	38.3 (11.9)	1.8 (0.7)	471 (132)	383 (119)	23.9 (7.1)

<sup>a</sup>C<sub>max</sub> = Maximum plasma concentration; T<sub>max</sub> = time of C<sub>max</sub>; AUC (0-24) = Area under the plasma concentration-time curve over the dosing interval; and CL/F = Apparent oral clearance; t<sub>1/2</sub> = Elimination half-life

<sup>b</sup>ND = Not determined

Based on a population pharmacokinetic analysis, average estimates of steady-state concentrations (C<sub>ss</sub>) of norethindrone and ethinyl estradiol in femHRT (NA/EE) tablets are shown in Table 3 below.

**Table 3. Average Steady-State Concentrations (C<sub>ss</sub>) of Norethindrone and Ethinyl Estradiol in NA/EE Tablets**

	mg NA/μg EE		
	0.5/2.5	1/5	1/10
Norethindrone (ng/mL)	1.1	2.6	2.9
Ethinyl Estradiol (pg/mL)	5.4	11.4	17.2

### Distribution

Volume of distribution of norethindrone and ethinyl estradiol ranges from 2 to 4 L/kg. Plasma protein binding of both steroids is extensive (>95%); norethindrone binds to both albumin and sex hormone binding globulin (SHBG), whereas ethinyl estradiol binds only to albumin. Although ethinyl estradiol does not bind to SHBG, it induces SHBG synthesis. femHRT increases serum SHBG concentrations approximately 2.6-fold over pretreatment values.

### Metabolism

Norethindrone acetate is rapidly deacetylated to norethindrone after oral administration, and the disposition of norethindrone acetate is indistinguishable from that of orally administered norethindrone. Norethindrone undergoes extensive biotransformation, primarily via reduction, followed by sulfate and glucuronide conjugation. The majority of metabolites in the circulation are sulfates, with glucuronides accounting for most of the urinary metabolites. A small amount of norethindrone acetate is metabolically converted to ethinyl estradiol, such that exposure to ethinyl estradiol following administration of 1 mg of norethindrone acetate is equivalent to oral administration of 2.8 mcg ethinyl estradiol. Ethinyl estradiol is also extensively metabolized, by both oxidation and by conjugation with sulfate and glucuronide. Sulfates are the major circulating conjugates of ethinyl estradiol and glucuronides predominate in the urine. The primary oxidative metabolite is 2-hydroxy ethinyl estradiol, formed by the CYP3A4 isoform of cytochrome

P450. Part of the first-pass metabolism of ethinyl estradiol is believed to occur in gastrointestinal mucosa. Ethinyl estradiol may undergo enterohepatic circulation.

### **Excretion**

Norethindrone and ethinyl estradiol are excreted in both urine and feces, primarily as metabolites. Plasma clearance values for norethindrone and ethinyl estradiol are similar (approximately 0.4 L/hr/kg). Steady-state elimination half-lives of norethindrone and ethinyl estradiol following administration of NA 1 mg/EE 10 µg tablets are approximately 13 hours and 24 hours, respectively.

### **Special Populations and Conditions**

#### **Geriatrics**

The pharmacokinetics of norethindrone acetate and ethinyl estradiol was not affected by age (age range 40-62), in the postmenopausal population studied.

#### **Hepatic Insufficiency**

The effect of hepatic disease on the disposition of femHRT has not been evaluated. However, ethinyl estradiol and norethindrone may be poorly metabolized in patients with impaired liver function (see CONTRAINDICATIONS).

#### **Renal Insufficiency**

The effect of renal disease on the disposition of femHRT has not been evaluated. In premenopausal women with chronic renal failure undergoing peritoneal dialysis who received multiple doses of an oral contraceptive containing ethinyl estradiol and norethindrone, plasma ethinyl estradiol concentrations were higher and norethindrone concentrations were unchanged compared to concentrations in premenopausal women with normal renal function.

### **STORAGE AND STABILITY**

Store at controlled room temperature, 15-25° C.

### **DOSAGE FORMS, COMPOSITION, AND PACKAGING**

femHRT 0.5/2.5 tablets are white, oval tablets, debossed with “PD” on one side and “145” on the other side, containing 0.5 mg norethindrone acetate and 2.5 µg ethinyl estradiol.

femHRT 1/5 tablets are white, D-shaped tablets, debossed with “WC” on one side and “144” on the other side, containing 1 mg norethindrone acetate and 5 µg ethinyl estradiol.

Package Size: Blister card of 28 tablets  
Bottles of 90 tablets

## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

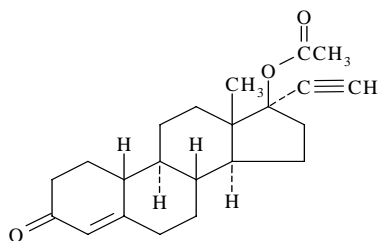
#### Drug Substance

##### Proper name: Norethindrone Acetate

Chemical name: (17a-) - 17 (acetyloxy)-19-norpregna-4-en-20-yne-3-one

Molecular formula and molecular weight:  $C_{22}H_{28}O_3$  and 340.46

Structural Formula:



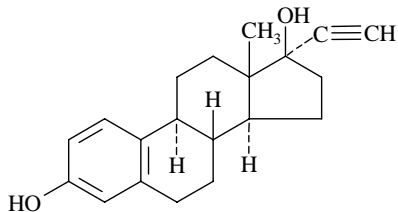
Physicochemical properties: A white solid with a melting point of 157° to 163°C, freely soluble in dioxane, sparingly soluble in ether, and insoluble in water

##### Proper name: Ethinyl estradiol

Chemical name: (17a) -19-norpregna-1,3,5(10)-trien-20-yne-3,17-diol

Molecular formula and molecular weight:  $C_{20}H_{24}O_2$  and 296.40

Structural Formula:



Physicochemical Properties: A fine white, odourless crystalline powder, insoluble in water but soluble in vegetable oils and organic solvents

## **CLINICAL TRIALS**

The safety and efficacy of femHRT (norethindrone acetate and ethinyl estradiol) have been studied in 2 placebo-controlled clinical trials of 12 to 16 weeks duration for treatment of vasomotor symptoms; a 2-year placebo-controlled study for vasomotor symptoms, prevention of osteoporosis and endometrial safety, and a 1-year reference-controlled study for confirming endometrial safety versus a frequently used estrogen-progestin combination of conjugated equine estrogen and medroxyprogesterone acetate (Premarin<sup>TM</sup>/MPA).

### **Vasomotor Symptoms**

Two placebo-controlled, multicentre, randomized clinical trials were conducted to determine the safety and efficacy of femHRT on reducing the frequency of hot flushes.

#### **A. Study 376-368**

In Study 376-368, the effect of femHRT in reducing vasomotor symptoms (frequency) was established in postmenopausal women (N=219, 188/219 completers), who reported symptoms during a 2-week baseline period, with a mean frequency of >40 hot flushes per week. Subjects received femHRT 0.5/2.5, 1/5, or placebo for a period of 16 weeks.

At the end of the study, both femHRT 0.5/2.5 and 1/5 groups differed significantly from placebo in mean reduction in frequency of hot flushes (Figure 2).

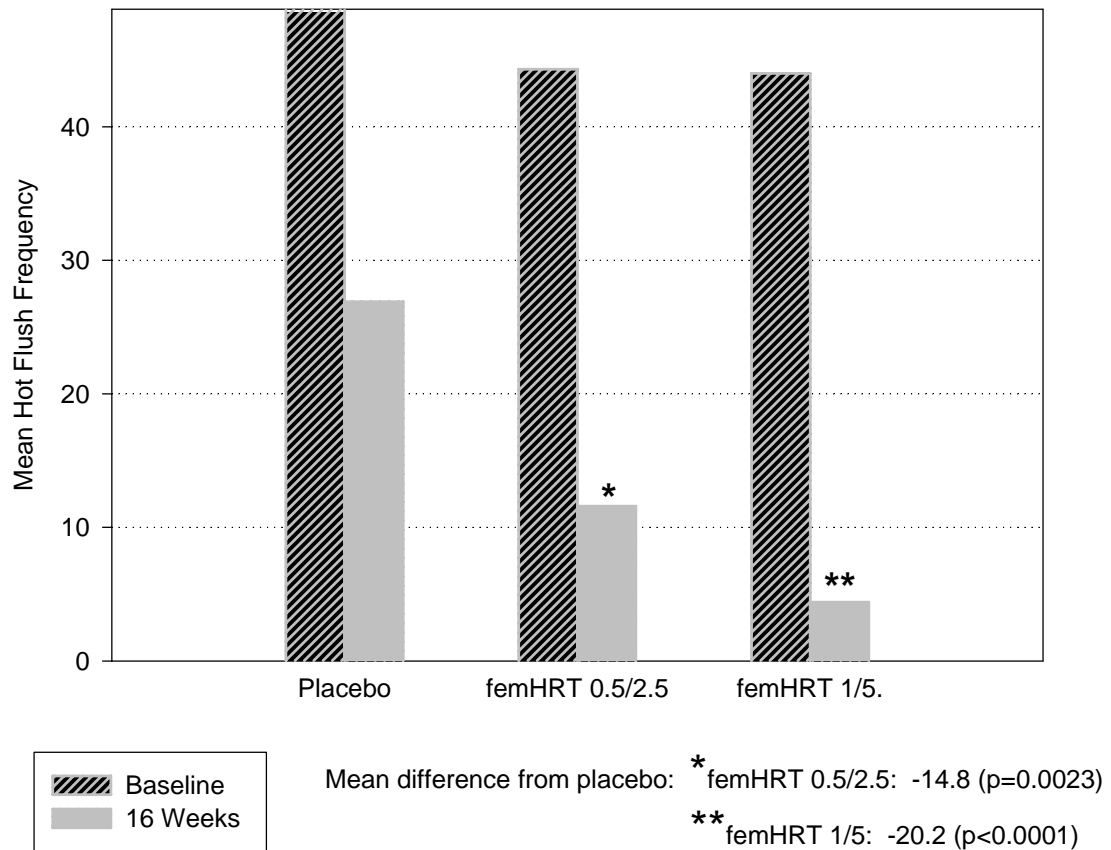


Figure 2. Reduction in Weekly Frequency of Hot Flushes: Mean Difference from Baseline for femHRT 0.5/2.5, 1/5, and Placebo Groups at Week 16 (Study 376-368)

### B. Study 376-390

A 12-week-placebo controlled, multicentre, randomized clinical trial was conducted in 266 symptomatic women (230/266 completers) who had at least 56 moderate to severe hot flushes during the week prior to randomization. On average, patients had 12 hot flushes per day upon study entry.

The efficacy of femHRT for the treatment of severe vasomotor symptoms (VMS) is demonstrated in Figure 3 (reduction in frequency of hot flushes) and Figure 4 (reduction in intensity of hot flushes). Reduction in mean frequency of hot flushes with femHRT was significantly greater than placebo from Weeks 2 and 3, for femHRT 1/5 and 0.5/2.5 doses, respectively. Similarly, reduction in mean intensity of hot flushes with femHRT

was significantly greater than placebo from Weeks 3 and 6, for femHRT 1/5 and 0.5/2.5 doses, respectively.

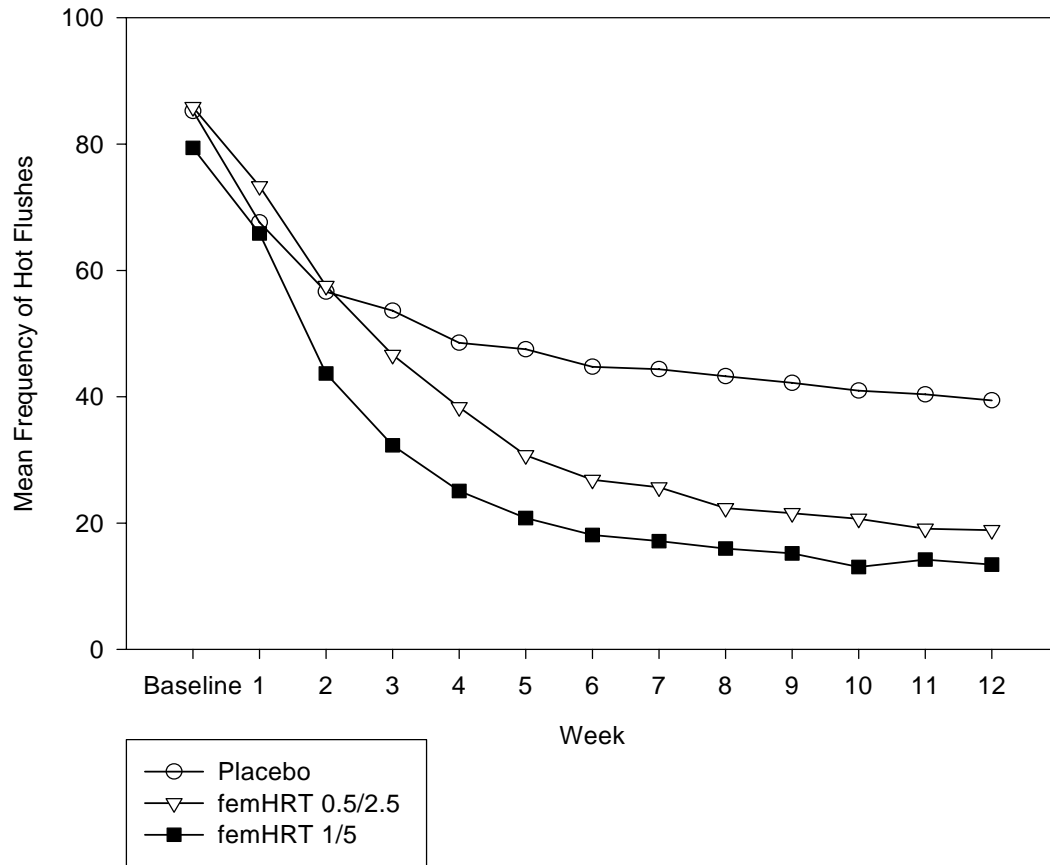


FIGURE 3. Mean Weekly Frequency of Hot Flashes by Treatment Group (Study 376-390)

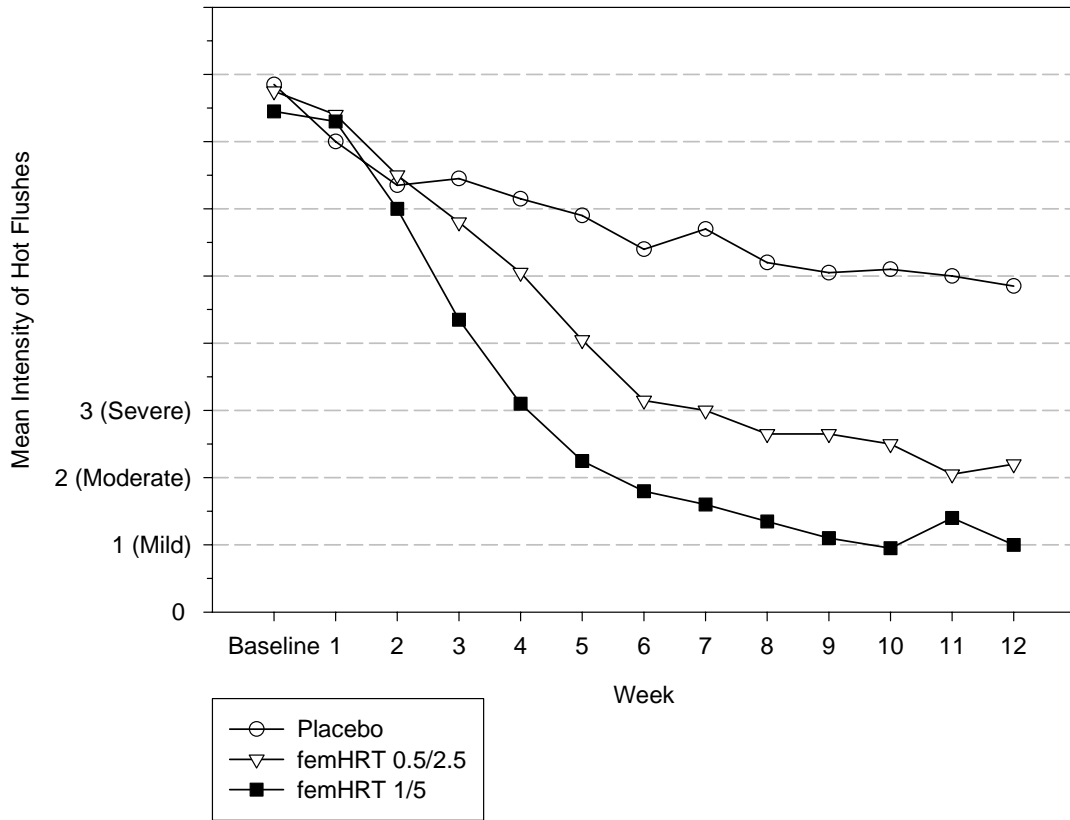


FIGURE 4. Mean Weekly Intensity of Hot Flashes by Treatment Group (Study 376-390)

## Effect on Bone Mineral Density

### A. Study 376-359

A 2-year, placebo-controlled, multicentre, randomized clinical trial was conducted to determine the safety and efficacy of various combinations of NA and EE on maintaining bone mineral density, protecting the endometrium, and to determine the effects on lipids. This trial is referred to as the CHART *Study* (376-359); *Continuous Hormones as Replacement Therapy*. Patients (n=1265, 822/1265 completers) were randomized to either placebo, femHRT 0.5/2.5, 1/5, or matching unopposed EE doses (2.5 or 5 µg). All participants received 1000 mg of elemental calcium supplement daily.

In the CHART *Study* (376-359), trabecular bone mineral density (BMD) was assessed at lumbar spine using quantitative computed tomography. Bone mineral density was maintained with femHRT 0.5/2.5 dose, while the NA/EE 1/5 dose resulted in a significant increase in BMD at each annual assessment. The increase in BMD seen with the femHRT 1/5 dose was statistically significantly different than the 5µg EE dose at Months 12 and 24. There was a significant decrease in BMD in the placebo group (Figure 5).

Over a 24-month treatment period, patients in the femHRT 0.5/2.5 and 1/5 groups had positive significant differences in BMD of 5.8 % (p=0.0026) and 9.8% (p=0.0001) respectively, versus the placebo group (absolute difference, adjusted mean % change from baseline). The changes in BMD versus the placebo group were 4.1% (p=0.0449) and 4.9% (p=0.0116), in patients receiving unopposed 2.5 and 5µg EE, respectively, over the same time period.

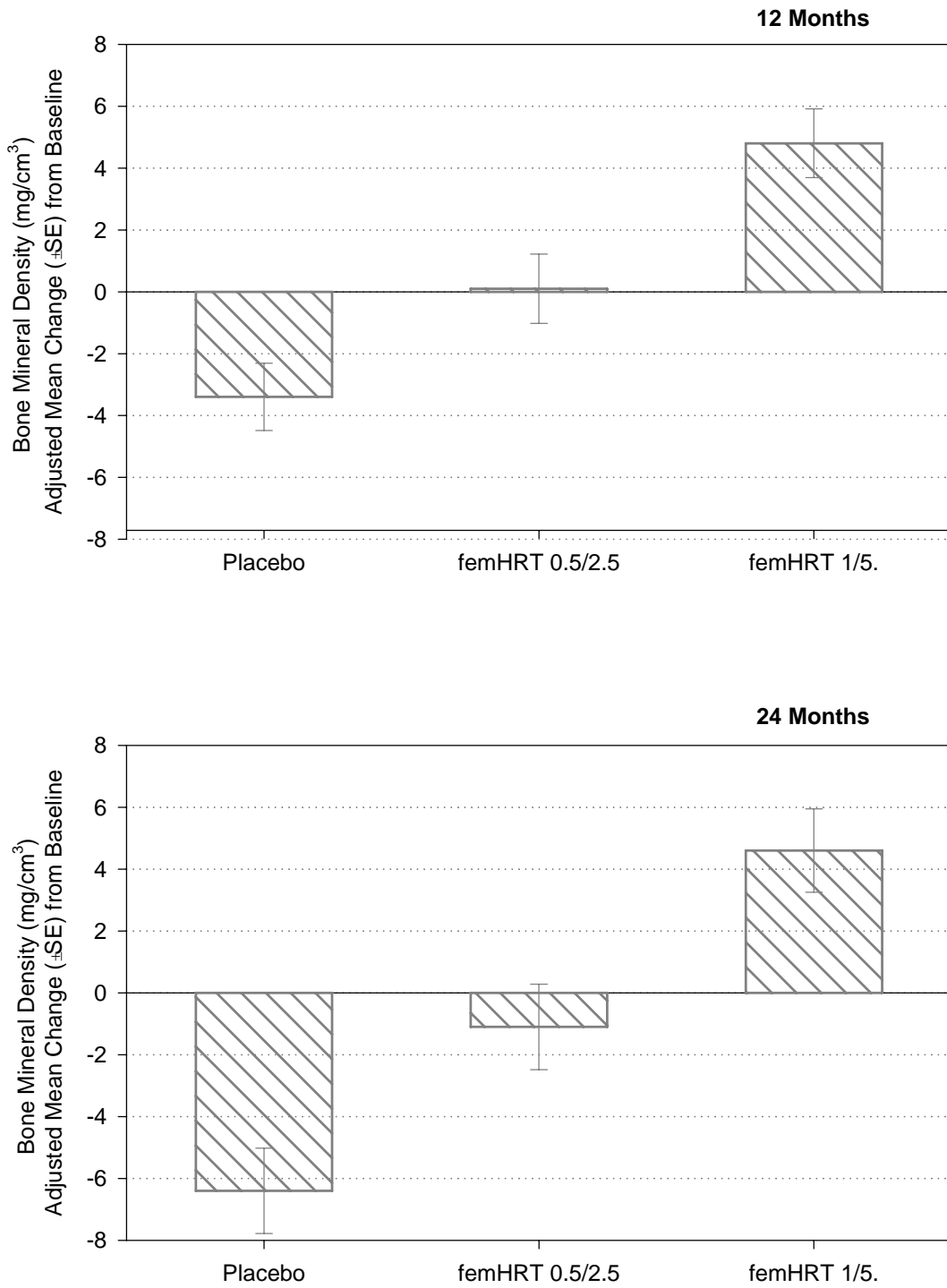


FIGURE 5. Bone Mineral Density (mg/cm<sup>3</sup>) Adjusted Mean Change (± SE) for Baseline at Month 12 and Month 24 (CHART Study, 376-359)

NA = Norethindrone acetate

EE = Ethinyl Estradiol

### Effects on Endometrium

**CHART Study (376-359):** Biopsies were obtained at 6-month intervals in the *CHART Study*. Baseline biopsies were classified as normal (in approximately 95% of subjects), or insufficient tissue (in approximately 5% of subjects). Follow-up biopsies were obtained in approximately 70-80% of patients in each arm of the study after 12 and 24 months of therapy. All unopposed EE groups reported at least 1 case of hyperplasia with the highest incidence at the highest dose. No hyperplasia was detected in any of the femHRT treatment groups (Table 4).

The extent of endometrial proliferation was quantified using Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM), and a severity score was assigned (1 = atrophic; 2 = mildly proliferative; 3 = moderately proliferative; 4 = markedly proliferative; 5 = hyperplastic). There was a dose-related increase in severity score with unopposed ethinyl estradiol use, while the endometrial status of all NA/EE dose combinations was similar to placebo.

**Table 4. Endometrial Biopsy Results After 12 and 24 Months of Treatment (CHART Study 376-359)**

Endometrial Status	Placebo	femHRT		EE Alone	
		0.5/2.5	1/5	2.5 µg	5 µg
<b>Number of Patients Biopsied at Baseline</b>	N = 134	N = 136	N = 143	N = 137	N = 139
<b>Month 12 (% Patients)</b>					
Patients Biopsied (%)	113 (84)	103 (74)	110 (77)	100 (73)	114 (82)
Insufficient Tissue	30	34	45	20	20
Atrophic tissue	60	41	41	15	2
Proliferative Tissue	23	28	24	65	91
Endometrial Hyperplasia <sup>a</sup>	0	0	0	0	1
<b>Month 24 (% Patients)</b>					
Patients Biopsied (%)	94 (70)	99 (73)	102 (71)	89 (65)	107 (77)
Insufficient Tissue	35	42	37	23	17
Atrophic tissue	38	30	33	6	2
Proliferative Tissue	20	27	32	60	86
Endometrial Hyperplasia <sup>a</sup>	1	0	0	0	2

<sup>a</sup>All patients with endometrial hyperplasia were carried forward for all time points.

### **Endometrial Safety Data from Study 376-401**

*Study 376-401* was a randomized, double-blind, comparative, 1-year multicentre study in healthy postmenopausal women (n=945, 657/945 completers), to assess the safety and protective effect on the endometrium, of femHRT 1/5, EE alone 5 µg, placebo, or 0.625 mg Premarin<sup>TM</sup>/2.5 MPA. In addition, all subjects received 1000 mg of elemental calcium supplement daily.

Endometrial biopsies were obtained at baseline and all subjects were required to have no evidence of either hyperplasia or markedly proliferative endometrial tissue in order to be eligible for the study. The results from this study replicate those obtained from the *CHART Study (376-359)*, i.e., at the end of 1 year no cases of hyperplasia were observed in subjects receiving femHRT 1/5. The additional experience from this comparative, controlled clinical trial provides further support for the protective endometrial effects of femHRT.

### **Bleeding and/or Spotting**

(i) *CHART Study (376-359)*: Figure 6 shows the incidence of bleeding and/or spotting, as determined after 24 month observations in the *CHART Study*. The number of femHRT patients reporting bleeding and/or spotting decreased steadily to 13% by end of the study.

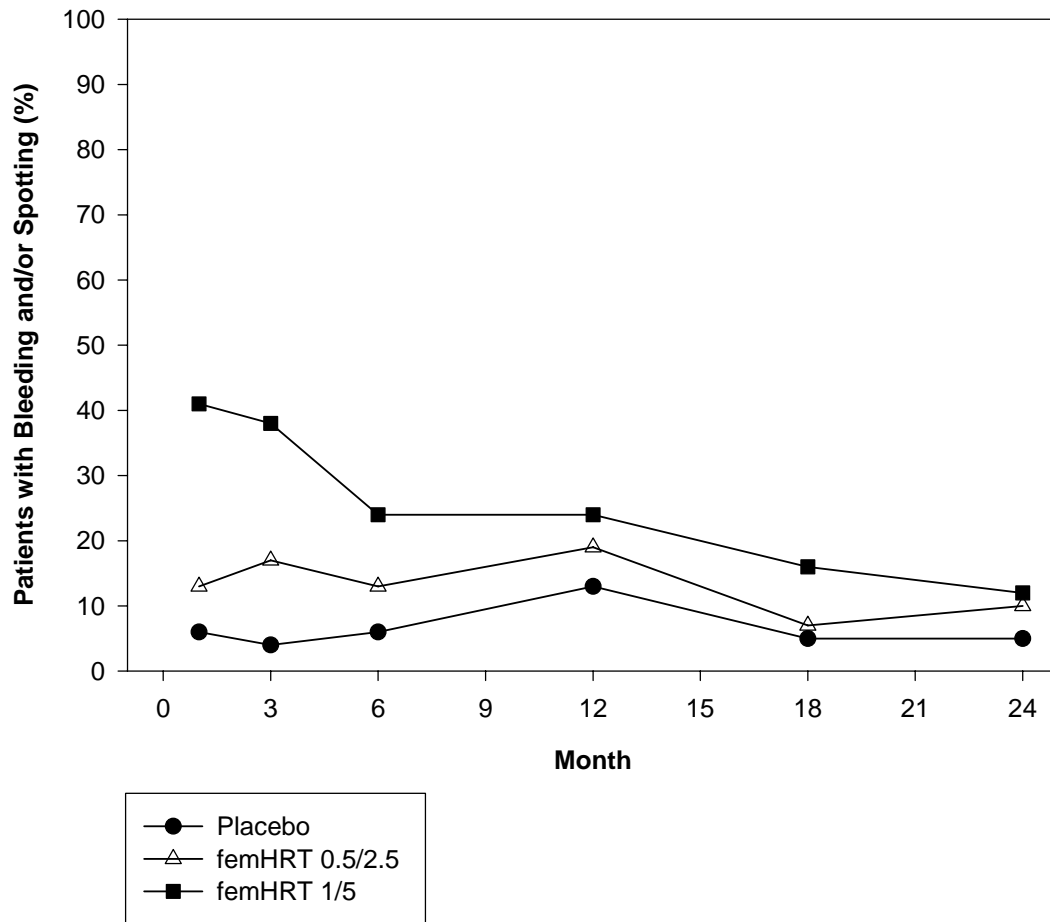


FIGURE 6: Incidence of Bleeding and/or Spotting with femHRT 0.5/2.5, 1/5 and Placebo (CHART Study 376-359)

(ii) **Study 376-401:** Figures 7 and 8 show the monthly incidence of bleeding only and bleeding/spotting, as determined after 12-month observations in the analysis of *Study 376-401*. After 6 months, the incidence of bleeding and/or spotting in *Study 376-401* was not significantly different between femHRT and placebo groups.

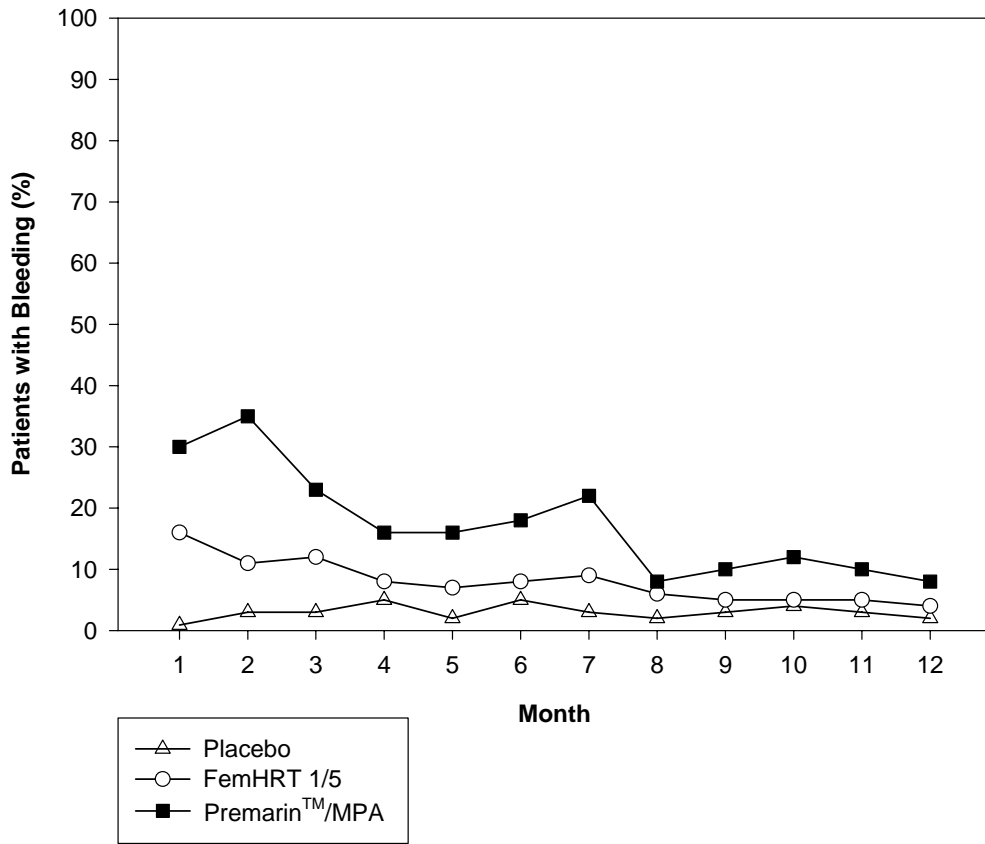


FIGURE 7: Monthly Incidence of Bleeding with femHRT 1/5, Placebo and Premarin™/MPA (Study 376-401, 12 Months)

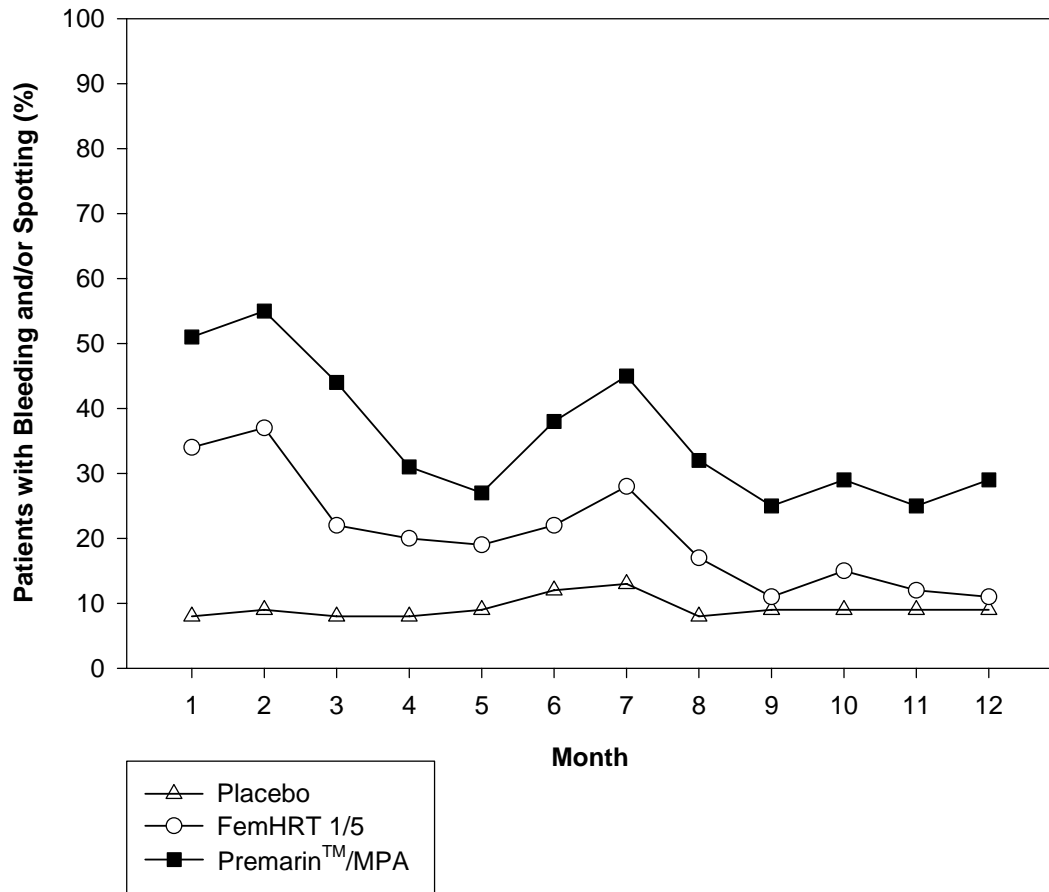


FIGURE 8. Monthly Incidence of Bleeding and/or Spotting with femHRT 1/5, Placebo and Premarin™/MPA (Study 376-401, 12 Months)

### Cumulative Amenorrhea

(i) In **Study 376-390**, the rate of amenorrhea, defined as no bleeding or spotting, was evaluated for femHRT 0.5/2.5, 1/5 and placebo groups over a 12-week period. By the end of the study, the cumulative percent of subjects who were amenorrheic in the femHRT 0.5/2.5 dose group (93%) and femHRT 1/5 dose group (87%) were similar to that in the placebo group (Figure 9).

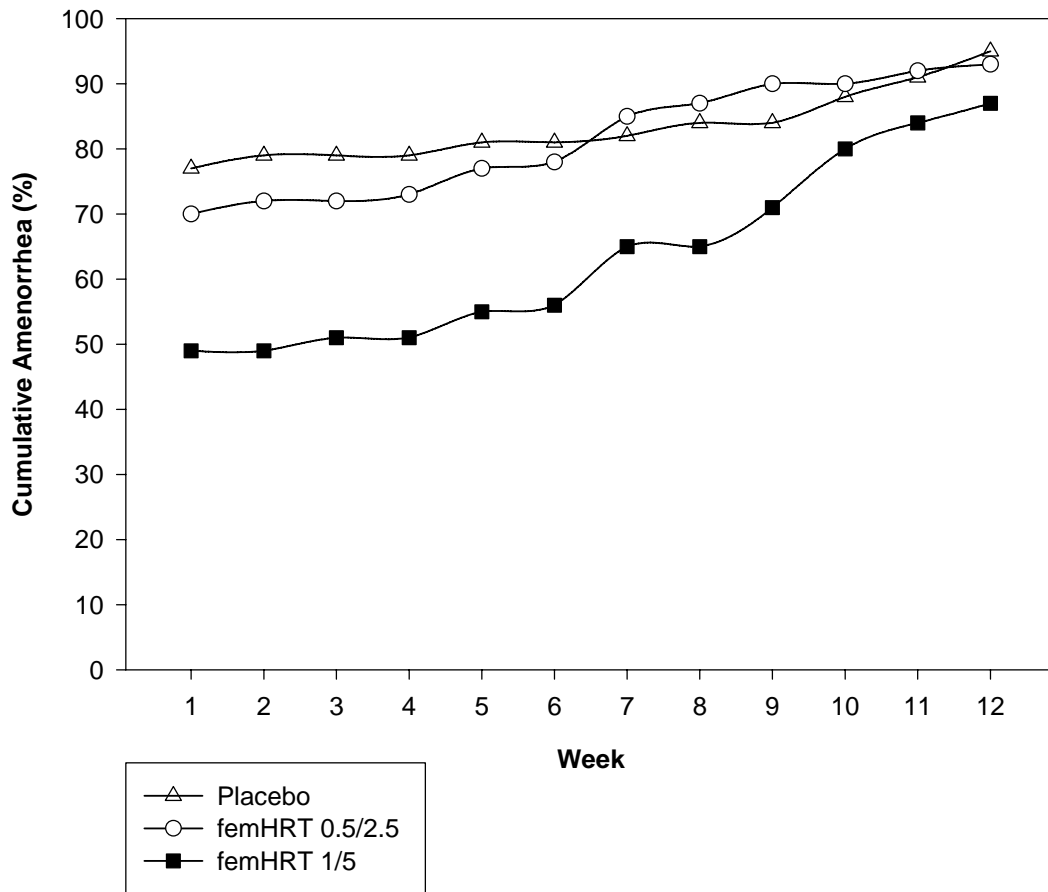


FIGURE 9. Percent of Patients with Cumulative Amenorrhea Over Time (Study 376-390)

(ii) **CHART Study (376-359):** The cumulative incidence of amenorrhea was evaluated over 24 months for femHRT 0.5/2.5, 1/5 and placebo arms. Results are shown in Figure 10.

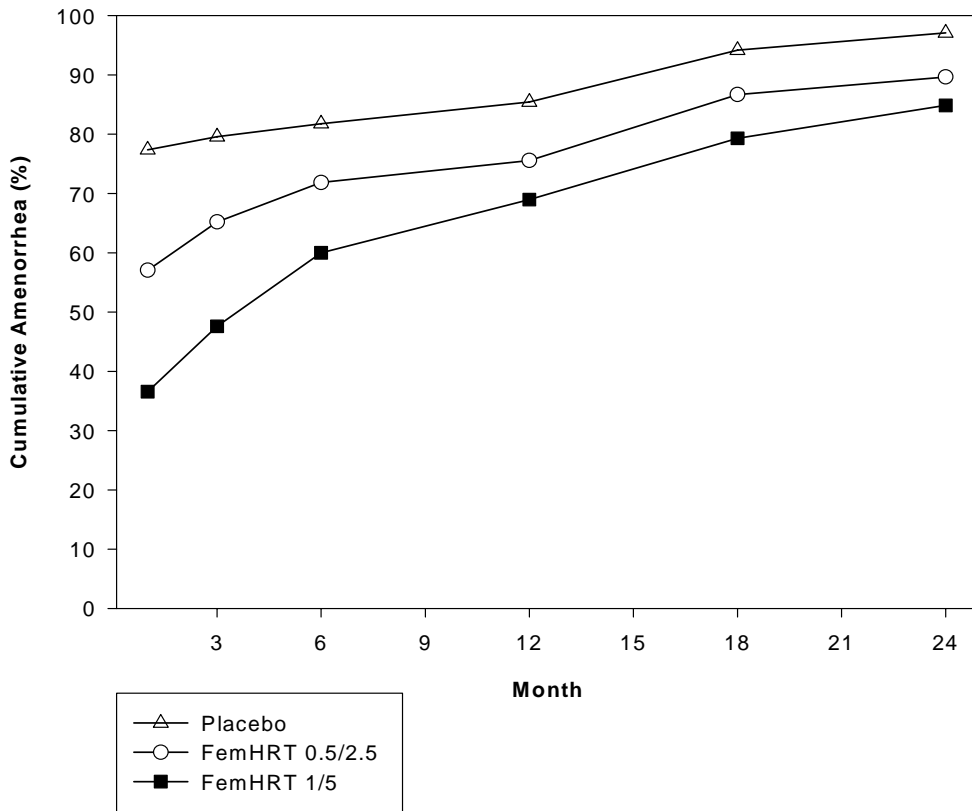


FIGURE 10. Patients with Cumulative Amenorrhea Over Time: Intent-To-Treat Population, Last Observation Carried Forward (*CHART Study, 376-359*)

**(ii) Study 376-401**

The cumulative incidence of amenorrhea was evaluated over 12 months for femHRT 1/5, placebo and Premarin<sup>TM</sup>/MPA groups in *Study 376-401*. The incidence of amenorrhea with femHRT 1/5 was not significantly different from placebo at Months 9 to 12. The incidence of amenorrhea in the femHRT 1/5 group was significantly different from the Premarin<sup>TM</sup>/MPA group at each monthly interval, from Months 1 to 12. Results are shown in Figure 11.

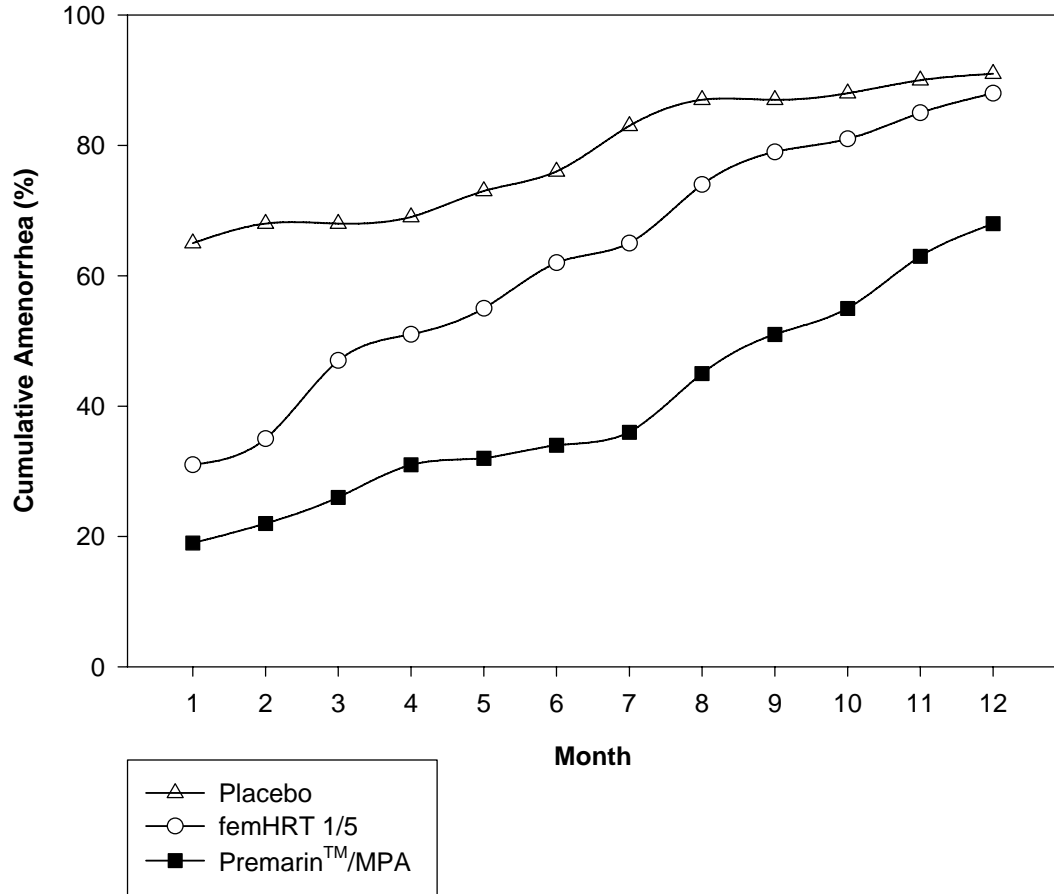


FIGURE 11. Patients With Cumulative Amenorrhea Over Time: Intent-To-Treat Population (Study 376-401)

## Effects on Lipids

In the *CHART Study* (376-359), femHRT 0.5/2.5 and 1/5 decreased total cholesterol and LDL-C. The elevation in triglycerides observed with unopposed ethinyl estradiol was attenuated with femHRT. Table 5 summarizes mean changes from baseline for each lipid parameter after 2 years of treatment with femHRT, unopposed ethinyl estradiol and the placebo group. In addition, the total cholesterol to HDL-C ratio is presented as an indicator of overall effect.

**Table 5. Mean % Change From Baseline Lipid Profile: Value After 2 Years of Treatment (*CHART Study*, 376-359)**

Lipid Parameter	Placebo	FemHRT (mg NA/ $\mu$ g EE)		Unopposed EE ( $\mu$ g EE)	
		0.5/2.5	1/5	2.5	5
	N=129	N=128	N=132	N=126	N=128
Total Cholesterol <sup>a</sup>	1.6	-5.4	-7.0	0.9	2.3
HDL-C <sup>a</sup>	1.3	-0.1	-6.7	11.7	18.5
LDL-C	1.0	-8.0	-7.5	-5.9	-6.8
Triglycerides <sup>a</sup>	19.1	8.0	12.1	29.7	38.7
Total Cholesterol/HDL-C	1.65	-3.57	1.89	-7.05	-10.96

NA = Norethindrone acetate

EE = Ethinyl Estradiol

HDL-C/LDL-C ratios increased in all femHRT treated subjects after 12 months and 24 months therapy, but did not appear to be dose-related. The atherogenic index, which was in the low-risk range for this age group (Total-C/HDL-C<4.5), remained stable in all femHRT treatment groups. Thus the overall effect of femHRT on the serum lipid profile in menopausal women was considered improved or neutral.

## Effects on Coagulation Parameters

In *Study 376-390*, Factor VII and plasminogen activator inhibitor-1 decreased from baseline in a dose-related manner, but remained within the normal laboratory reference range for postmenopausal women who were randomized to femHRT. Fibrinogen and partial thromboplastin time did not change from baseline for any of the NA/EE combination groups.

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## **PART III: CONSUMER INFORMATION**

### **Information for Patients Using femHRT<sup>®</sup> as Hormone Replacement Therapy**

Please read this PATIENT INFORMATION before you start taking femHRT and each time you refill femHRT. 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.

#### **About this medication. What is femHRT?**

##### **What the medication is used for**

- *To relieve Menopausal Symptoms and vaginal itching associated with menopause* – As the level of estrogen production falls during menopause, some women experience hot flashes. A hot flush is a sudden onset of heat spreading over the face, neck and/or chest causing the skin to redden and perspire. Hot flashes often occur at night and are called “night sweats”. Night sweats can cause sleep disturbances, which may lead to fatigue, irritability and depression. Estrogen loss can also cause changes in and around the vagina, which can lead to itching, burning, dryness, and painful intercourse. You and your healthcare provider should talk regularly about whether you still need treatment with femHRT.
- *To prevent thinning of bones (Osteoporosis)* – After menopause, all women start to lose calcium from their bones. Over time, this can lead to thinning of the bones, called osteoporosis, which makes them weaker and more likely to break. If you use femHRT only to prevent osteoporosis from menopause, talk with your healthcare provider about whether a different treatment or medicine without estrogens may be better for you. You and your healthcare provider should talk regularly about whether you should continue taking femHRT.

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.

##### **When it should not be used**

You should not take femHRT:

- If you are pregnant or may be pregnant
- If you are breastfeeding

- If you have undiagnosed or abnormal vaginal bleeding
- If you currently have or have had certain cancers. Estrogens increase the risk of certain types of cancers including cancer of the breast and uterus. If you have or had cancer, talk with your doctor about whether you should take femHRT.
- If you have endometrial hyperplasia (overgrowth of the uterus lining)
- If you have had or have any blood circulation problems including blood clots
- If you have a history of heart attack, heart disease or stroke
- If you have migraine headaches
- If you have had any loss of vision due to blood vessel disease in the eye
- In the presence of liver disease
- If you have had a hysterectomy (uterus removed)
- If you have had an allergic response to estrogen or progestin treatment

### **What the medicinal ingredients are**

Ethinyl estradiol and norethindrone acetate

### **What the important non-medicinal ingredients are**

femHRT tablets also contain calcium stearate, cornstarch, lactose monohydrate, and microcrystalline cellulose.

### **What dosage form it comes in**

femHRT 0.5/2.5 is supplied in an oval, white pill, which contains 0.5 milligram of norethindrone acetate (which is the progesterone portion of the pill, and is called a “progestin”) and 2.5 micrograms of ethinyl estradiol (the estrogen portion of the pill).

femHRT 1/5 is supplied in a D-shaped white pill, which contains 1 milligram of norethindrone acetate (which is the progesterone portion of the pill, and is called a “progestin”) and 5 micrograms of ethinyl estradiol (the estrogen portion of the pill).

### **Warnings and Precautions**

#### **Serious Warnings and Precautions**

<p><b>What is the most important information I should know about femHRT (a combination of estrogen and progestin hormones)?</b></p> <ul style="list-style-type: none"><li>• Do not use estrogens and progestins to prevent heart disease, heart attacks, or strokes.</li><li>• femHRT should be used at the lowest effective dose for the shortest period.</li><li>• Using estrogens and progestins may increase your risk of heart attack, stroke, breast cancer, and blood clots in the legs and lungs. You and your healthcare provider should talk regularly about whether you still need treatment with femHRT.</li></ul>
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- *Heart Disease and Stroke* – femHRT should not be used to treat or prevent heart disease or stroke. Studies show that taking estrogen/progestin therapy may increase your risk of heart disease or stroke.
- *Cancer of the breast* – Studies show that taking estrogen/progestin therapy may increase your risk for getting breast cancer. All women, and especially those who are at an increased risk of breast cancer because of a strong family history, presence of breast lumps, fibrocystic breast disease, or abnormal mammograms, should discuss the use of HRT with their doctor. You should have regular breast examinations by a health professional and examine your own breasts monthly. You may be advised to have a mammogram (breast x-ray) prior to the start of your treatment with femHRT and at regular intervals during treatment, as deemed appropriate by your doctor.
- *Cancer of the uterus and endometrial hyperplasia* – femHRT contains both an estrogen and progestin. Women who have not had surgical removal of the uterus (hysterectomy) require the addition of a progestin to estrogen, as in femHRT, to reduce the risk of overgrowth of the lining of the uterus (endometrial hyperplasia). Endometrial hyperplasia can lead to the development of cancer of the uterus.

If you take any drug that contains estrogen, including femHRT, you should see your doctor for regular check-ups and report any abnormal vaginal bleeding to your doctor right away. Your doctor should identify the cause of any unusual vaginal bleeding. Vaginal bleeding after menopause may be a warning sign of a serious condition including cancer of the uterus.

- *Gallbladder disease* – Studies have shown that there may be an increased risk of gallbladder disease with the use of estrogen during menopause.
- *Abnormal blood clotting* – Taking estrogens may cause changes in your blood clotting system that allow the blood to clot more easily. If blood clots form in your bloodstream, they can cut off the blood supply to vital organs, causing serious problems. These problems may include a stroke (by cutting off blood to the brain), a heart attack (by cutting off blood to the heart), or a pulmonary embolus (by cutting off blood supply to the lungs). Any of these conditions may cause death or serious long-term disability.
- *Dementia* – Current studies indicate that the use of combined hormone therapy in women age 65 and over may increase the risk of developing probable dementia (loss of memory and intellectual function).

## **Precautions**

As with any new therapy, your doctor will probably want to see you 3 to 6 months after starting femHRT. After that, you should see your doctor at least once a year for a physical examination, including a Pap test and breast examination.

- See your healthcare provider regularly. **Talk with your healthcare provider regularly (every 3-6 months) about whether you should continue taking femHRT.**
- See your healthcare provider right away if you develop vaginal bleeding while taking femHRT.
- 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 ever had breast lumps or an abnormal mammogram (breast x-ray), you may need more frequent breast examinations.**
- If you have high blood pressure, high cholesterol (fat in the blood), diabetes, are overweight, or use tobacco, you may have higher chances for getting heart disease. **Ask your healthcare provider for ways of lowering your chances for getting heart disease.**

If you notice any of the following symptoms, you should contact your doctor immediately:

- Lump in the breast
- Pain, or swollen veins, i.e., varicose veins
- Pain, tenderness, swelling, or redness in your legs
- Trouble breathing or tightness of the chest
- Severe or persistent nausea, vomiting and tenderness in the abdomen
- Severe headache, dizziness, faintness, weakness or changes in vision or speech
- Yellowing of the eyes or skin

Don't forget to do regular breast self-examinations every month and report any changes to your physician. After the age of 50, or earlier as recommended by your doctor, a mammogram (breast x-ray) is recommended every 1-2 years.

### **Interactions with this Medication**

Some drugs may affect the activity of femHRT, and it is important that your doctor or pharmacist knows all of the medications, which you are taking. Consult your doctor or pharmacist before taking any other medication, including non-prescription drugs and herbal remedies.

### **Usual Dose**

femHRT must only be taken under the supervision of your doctor. femHRT is very simple to take – one pill, once a day, every day. You can take femHRT any time of day, with or without food. However, it's usually easier to plan to take it at the same time each day; for example, just after brushing your teeth or before you go to bed.

## **Overdose**

**Symptoms:** Overdosage with estrogen or progestin containing products may cause nausea, breast discomfort, fluid retention, bloating, vaginal bleeding, depressed mood, tiredness, acne and hirsutism (abnormal or excessive hair growth).

**Treatment:** In case of overdose call your doctor, hospital, or poison control centre immediately.

## **Missed Dose**

If you forget to take your pill at the usual time, take it as soon as you remember. If it is almost time for your next pill, skip the missed pill and take the next one in the pack. Do not take two pills at once.

Hormone replacement therapy should only be used as long as needed. You and your healthcare provider should re-evaluate every 3-6 months whether or not you still need treatment with femHRT.

## **Side Effects and What to do About Them**

HRT is an effective treatment that has been used for over 50 years. The following side effects have been reported with femHRT and are similar to reports with other HRT products. Speak to your doctor if you experience:

- Nausea and vomiting
- Breast tenderness or enlargement
- Enlargement of uterine fibroids (benign growths in the uterus)
- Headache
- Retention of extra fluid (edema)
- Spotty darkening of the skin
- Abdominal pain

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

## **How to store it**

femHRT should be stored at controlled room temperature, 15-25° C.

## **More Information**

### **Will I have a monthly menstrual period?**

No, but you may notice some light bleeding or spotting for the first few months when taking femHRT. This is normal and occurs because the endometrium (lining of the

uterus) is adjusting to the hormones. With femHRT, bleeding normally stops during the first 3 to 6 months of therapy. If you experience vaginal bleeding while taking femHRT, discuss your bleeding pattern with your doctor. Any undiagnosed or unusual vaginal bleeding should be investigated by your doctor.

**Will I gain weight with femHRT?**

In clinical studies, women on femHRT did not gain any more weight than women who were not on femHRT.