PRODUCT MONOGRAPH

FEMHRT
(Norethindrone Acetate and Ethinyl Estradiol Tablets)
1 mg and 5 µg

FEMHRT LO
(Norethindrone Acetate and Ethinyl Estradiol Tablets)
0.5 mg and 2.5 µg

Estrogen-Progestin Combination

Warner Chilcott Canada Co.
Toronto, Ontario M5W 3N7

Date of Preparation: March 4, 2011

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tablet 0.5mg norethindrone acetate (NA) and 2.5µg ethinyl estradiol (EE) or 1 mg norethindrone acetate (NA) and 5 µg ethinyl estradiol (EE)	Lactose monohydrate *For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING.*

INDICATIONS AND CLINICAL USE

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

femHRT and femHRT Lo are 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 adequate diet, 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. (see also ACTIONS AND CLINICAL PHARMACOLOGY, General)

femHRT and femHRT Lo are recommended for use only in patients with an intact uterus, since the regimen includes a progestin whose role is to prevent endometrial hyperplasia.

CONTRAINDICATIONS

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

- Liver dysfunction or disease as long as liver function tests have failed to return to normal
- Known, suspected, or past history of breast cancer
- Known or suspected estrogen/progestin-dependent malignant neoplasia, (e.g. 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 vascular disease
- Known or suspected hypersensitivity to any components of the medication. For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING.

WARNINGS AND PRECAUTIONS

SERIOUS WARNINGS AND PRECAUTIONS

.The Women's Health Initiative (WHI) trial examined the health benefits and risks of oral combined *estrogen plus progestin* therapy (n=16,608) and oral *estrogen-alone* therapy (n=10,739) in postmenopausal women aged 50 to 79 years.
The *estrogen plus progestin* arm of the WHI trial (mean age 63.3 years) indicated an increased risk of *myocardial infarction* (MI), *stroke, invasive breast cancer, pulmonary emboli* and *deep vein thrombosis* in postmenopausal women receiving treatment with combined conjugated equine estrogens (CEE, 0.625 mg/day) and medroxyprogesterone acetate (MPA, 2.5 mg/day) for 5.2 years compared to those receiving placebo.
The *estrogen-alone* arm of the WHI trial (mean age 63.6 years) indicated an increased risk of *stroke* and *deep vein thrombosis* in hysterectomized women treated with CEE-alone (0.625 mg/day) for 6.8 years compared to those receiving placebo.
Therefore, the following should be given serious consideration at the time of prescribing:

- Estrogens with or without progestins **should not** be prescribed for primary or secondary prevention of cardiovascular diseases.
- Estrogens with or without progestins should be prescribed at **the lowest effective dose** for the approved indication.

- Estrogens with or without progestins should be prescribed for **the shortest period** possible for the approved indication.
- 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.

Carcinogenesis and Mutagenesis

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

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

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

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

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

It is recommended that estrogens with or without progestins not be given to women with existing breast cancer or those with a previous history of the disease (see CONTRAINDICATIONS).

There is a need for caution in prescribing estrogens with or without progestins for women with known risk factors associated with the development of breast cancer, such as strong family history of breast cancer (first degree relative) or who present a breast condition with an increased risk (abnormal mammograms and/ or atypical hyperplasia at breast biopsy).

Other known risk factors for the development of breast cancer such as nulliparity,obesity, early menarche, late age at first full term pregnancy and at menopause should also be evaluated.

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

The overall benefits and possible risks of hormone replacement therapy should be fully considered and discussed with patients. It is important that the modest increased riskof

being diagnosed with breast cancer after 4 years of treatment with combined estrogen plus progestin HRT (as reported in the results of the WHI trial) be discussed with the patient and weighed against its known benefits.

Instructions for regular self-examination of the breasts should be included in this counselling.

Two breast neoplastic events occurred across the four pivotal femHRT and/or femHRT Lo 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. Tumour 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.

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 and femHRT Lo provide 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 Lo (0.5/2.5) or femHRT (1/5) doses administered for 2 years. femHRT Lo (0.5/2.5) and femHRT (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.

Ovarian Cancer
Recent epidemiologic studies have found the use of HRT (estrogen-alone and estrogen plus progestin therapies), in particular for five or more years, has been associated with an increased risk of ovarian cancer.

Cardiovascular

The results of the Heart and Estrogen/progestin Replacement Studies (HERS and HERS II) and the Women's Health Initiative (WHI) trial indicate that the use of estrogen plus progestin is associated with an increased risk of coronary heart disease (CHD) in

postmenopausal women. The results of the WHI trial indicate that the use of estrogen-alone and estrogen plus progestin is associated with an increased risk of stroke in postmenopausal women.

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

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

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

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

HERS and HERS II findings
In the Heart and Estrogen/Progestin Replacement Study (HERS) of postmenopausal women with documented heart disease (n=2763, average age 66.7 years), a randomized placebo-controlled clinical trial of secondary prevention of coronary heart disease (CHD), treatment with 0.625 mg/day oral conjugated equine estrogen (CEE) plus 2.5 mg oral medroxyprogesterone acetate (MPA) demonstrated no cardiovascular benefit. Specifically, during an average follow-up of 4.1 years, treatment with CEE plus MPA did not reduce the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the hormone treated group than in the placebo group in year 1, but not during the subsequent years.
From the original HERS trial, 2321 women consented to participate in an open label extension of HERS known as HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. After 6.8 years, hormone therapy did not reduce the risk of cardiovascular events in women with CHD.

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

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

Blood Pressure
Women using HRT 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 or femHRT Lo therapy may have to be discontinued.

Ear, Nose and Throat

Otosclerosis
Estrogens should be used with caution in patients with otosclerosis.

Endocrine and Metabolism

Calcium and phosphorus metabolism
Because the prolonged use of estrogens influences the metabolism of calcium and phosphorus, estrogens with or without progestins should be used with caution in patients with metabolic and malignant bone diseases associated with hypercalcemia and in patients with renal insufficiency.

Glucose and lipid metabolism
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 need special surveillance. Lipid lowering measures are recommended before starting treatment in these women.

Heme metabolism
Women with porphyria need special surveillance.

Hypothyroidism
Patients who require thyroid HRT and who are also taking estrogen should have their thyroid function monitored regularly to assure that thyroid hormone levels remain in an acceptable range (see **Monitoring and Laboratory Tests**).

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

Genitourinary

Vaginal bleeding
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.

Uterine leiomyomata
Pre-existing uterine leiomyomata 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 leiomyomata requires prompt attention and, if necessary, discontinuation of medication.

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

Hematologic

Venous thromboembolism
Available epidemiological data indicate that the use of estrogen with or without progestin is associated with an increased risk of developing venous thromboembolism (VTE). In the estrogen plus progestin arm of the WHI trial, among 10,000 women on combined HRT over a one-year period, there were 18 more cases of venous thromboembolism, including 8 more cases of pulmonary embolism.

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

One venous thromboembolic event occurred across the four pivotal femHRT and femHRT Lo 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 kg/m^2) and systemic lupus erythematosus. The risk of VTE also increases with age and smoking.

The risk of VTE may be temporarily increased with prolonged immobilization, major surgery or trauma. In women on HRT, attention should be given to prophylactic measures to prevent VTE following surgery. Also, patients with varicose veins should be closely supervised. The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, retinal thrombosis, cerebral embolism and pulmonary embolism). If these occur or are suspected, femHRT or femHRT Lo therapy should be discontinued immediately, given the risks of long-term disability or fatality.

If feasible, HRT should be discontinued at least 4 weeks before major surgery or during periods of prolonged immobilization

Hepatic/Biliary/Pancreatic

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

Hepatic hemangioma
Particular caution is indicated in women with hepatic hemangiomas as estrogens may cause an exacerbation of this condition.

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

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

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

Immune

Systemic lupus erythematosus
Particular caution is indicated in women with systemic lupus erythematosus.

Neurologic

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

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

Dementia
Available epidemiological data indicate that the use of combined estrogen plus progestin in women age 65 and over may increase the risk of developing probable dementia.
The Women's Health Initiative Memory Study (WHIMS), a clinical substudy of the WHI, was designed to assess whether postmenopausal HRT (oral estrogen plus progestin or oral estrogen-alone) reduces the risk of dementia in women aged 65 and over (age range 65-79 years) and free of dementia at baseline.

In the estrogen plus progestin arm of the WHIMS (n=4532), women with intact uteri were treated with daily 0.625 mg conjugated equine estrogens (CEE) plus 2.5 mg medroxyprogesterone acetate (MPA) or placebo for an average of 4.05 years. The results, when extrapolated to 10,000 women treated over a one-year period showed 23 more cases of probable dementia (45 on combined HRT versus 22 on placebo).

In the estrogen-alone arm of the WHIMS (n=2947), women with prior hysterectomy were treated with daily 0.625 mg CEE or placebo for an average of 5.21 years. The results, when extrapolated to 10,000 women treated over a one-year period showed 12 more cases of probable dementia (37 on estrogen-alone versus 25 on placebo), although this difference did not reach statistical significance.

When data from the estrogen plus progestin arm of the WHIMS and the estrogen alone arm of the WHIMS were combined, as per the original WHIMS protocol, in 10,000 women over a one-year period, there were 18 more cases of probable dementia (41 on estrogen plus progestin or estrogen-alone versus 23 on placebo).

Epilepsy
Particular caution is indicated in women with epilepsy, as estrogens with or without progestins may cause an exacerbation of this condition.

Renal

Estrogens with or without progestins may cause fluid retention. Therefore, particular attention is indicated in cardiac or renal dysfunction or asthma. If, in any of the above-mentioned conditions, a worsening of the underlying disease is diagnosed or suspected during treatment, the benefits and risks of treatment should be reassessed based on the individual case.

The effect of renal disease on the disposition of femHRT and femHRT Lo 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):
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

Before femHRT or femHRT Lo (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, only when indicated. Baseline tests should include mammography, measurements of blood glucose, calcium, triglycerides and cholesterol, and liver function tests.

The first follow-up examination should be done within 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.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

See WARNINGS AND PRECAUTIONS regarding potential induction of malignant neoplasms and adverse effects similar to those of oral contraceptives.

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

Blood and lymphatic system disorders: Altered coagulation tests (see Warnings and Precautions, Drug-Laboratory Tests Interactions).

Cardiac disorders: Palpitations; increase in blood pressure (see Warnings and Precautions); coronary thrombosis.

Endocrine disorders: Increased blood sugar levels; decreased glucose tolerance.

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

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

General disorders and administration site conditions: Fatigue; changes in appetite; changes in body weight; change in libido.

Hepatobiliary disorders: Gallbladder disorder; asymptomatic impaired liver function; cholestatic jaundice.

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

Nervous system disorders: Aggravation of migraine episodes; headaches; dizziness; neuritis.

Psychiatric disorders: Mental depression; nervousness; irritability.

Renal and urinary disorders: Cystitis; dysuria; sodium retention; edema.

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

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

Vascular disorders: Isolated cases of: thrombophlebitis; thromboembolic disorders.

Clinical Trial Adverse Drug Reactions

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

Adverse events reported in placebo controlled clinical studies of femHRT or femHRT Lo at a frequency of ≥ 5% are shown in Table 1 below.

Table 1. All Treatment-Emergent Adverse Events Reported at a Frequency of ≥ 5% of Patients with femHRT or femHRT Lo

BODY SYSTEM/ Adverse Event	Percent of Patients (%)		
	Placebo	femHRT Lo	femHRT
	N = 247	N =244	N = 258
BODY AS A WHOLE	**40.1**	**38.5**	**39.5**
Headache	**14.6**	**15.2**	**18.2**
Back Pain	**5.3**	**5.3**	**4.7**
Viral Infection	**7.7**	**8.6**	**7.0**
DIGESTIVE SYSTEM	**24.4**	**30.5**	**33.0**
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**

BODY SYSTEM/ Adverse Event	Percent of Patients (%)		
	Placebo	femHRT Lo	femHRT
MUSCULOSKELETAL SYSTEM	**21.7**	**20.3**	**20.4**
Arthralgia	**6.9**	**2.9**	**5.8**
Myalgia	**8.5**	**8.6**	**7.8**
PSYCHOBIOLOGIC FUNCTION	**8.3**	**7.9**	**14.1**
Nervousness	**1.6**	**1.6**	**5.4**
Depression	**3.6**	**3.7**	**5.8**
RESPIRATORY SYSTEM	**37.2**	**33.9**	**35.6**
Rhinitis	**15.4**	**12.7**	**15.1**
Sinusitis	**9.7**	**9.4**	**8.1**
UROGENITAL SYSTEM	**25.0**	**31.6**	**40.8**
Breast Pain	**5.3**	**9.0**	**8.1**
Urinary Tract Infection	**3.2**	**3.7**	**6.2**
Vaginitis	**4.9**	**4.5**	**5.4**

DRUG INTERACTIONS

Overview

No drug-drug interaction studies have been conducted with femHRT or femHRT Lo. 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, femHRT Lo, 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, meprobamate, 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 and femHRT Lo 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.

Drug-Laboratory Interactions

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

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

- impaired glucose tolerance;
- increased serum triglycerides and phospholipids concentration;

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

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

DOSAGE AND ADMINISTRATION

Dosing Considerations

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

Treatment of Vasomotor Symptoms
femHRT Lo or femHRT 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.

Symptomatic Treatment of Vulvar and Vaginal Atrophy Associated with Menopause
femHRT Lo or femHRT 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.

Prevention of Osteoporosis
femHRT Lo or femHRT 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.

For management of suspected drug overdose, contact your regional Poison Control Centre.

ACTIONS AND CLINICAL PHARMACOLOGY

General

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 weigh-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.

Mechanism of Action

femHRT and femHRT Lo (norethindrone acetate and ethinyl estradiol, NA/EE) are each continuous dosage regimens of an estrogen-progestin combination for oral administration as hormone replacement therapy (HRT). femHRT and femHRT Lo manage 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 HRT 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 and femHRT Lo tablets is similar to that from solution for norethindrone and slightly less for ethinyl estradiol absorption. Administration of femHRT or femHRT Lo 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 Lo and femHRT 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 Lo and femHRT tablets are proportional to dose, but there is a less than proportional increase in steady state concentration for the NA/EE 1/10 tablet.

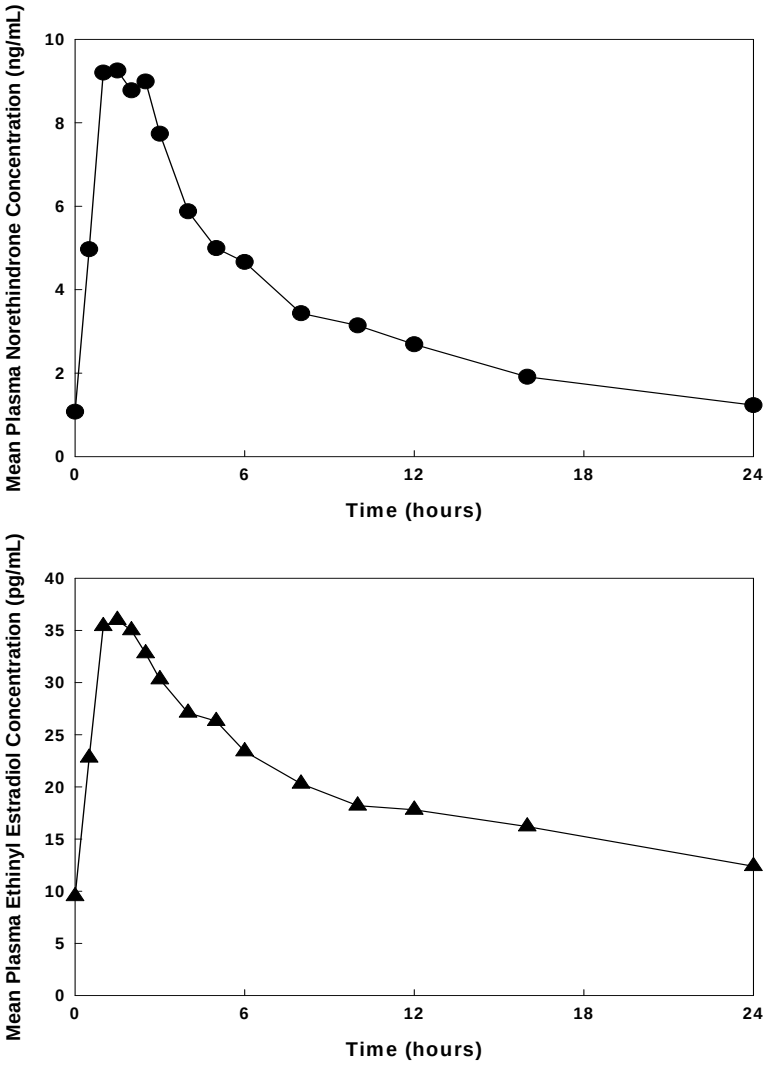


FIGURE 1. Mean Steady-State (Day 87) Plasma Norethindrone and Ethinyl Estradiol Concentrations Following Chronic Adminstration of NA 1mg/EE 10 µg Tablets.

Table 2. Mean (SD) Single-Dose (Day 1) and Steady-State (Day 87) Pharmacokinetic Parameters[a] 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)	NDb	NDb
Day 87	38.3 (11.9)	1.8 (0.7)	471 (132)	383 (119)	23.9 (7.1)

[a]C_{max} = Maximum plasma concentration; T_{max} = time of C_{max}; AUC (0-24) = Area under the plasma concentration-time curve over the dosing interval; and CL/F = Apparent oral clearance; $t_{1/2}$ = Elimination half-life
[b]ND = Not determined

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

Table 3. Average Steady-State Concentrations (Css) 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 µg 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 or femHRT Lo 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 or femHRT Lo 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 Lo tablets are white, oval tablets, debossed with “WC” on one side and “145” on the other side, containing 0.5 mg norethindrone acetate and 2.5 µg ethinyl estradiol.

femHRT 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

Non-medicinal Ingredients
femHRT and femHRT Lo tablets also contain calcium stearate, cornstarch, lactose monohydrate, and microcrystalline cellulose.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

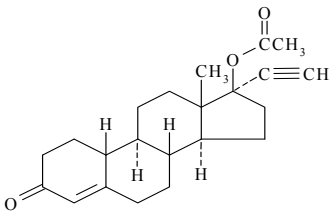
Drug Substance

Proper name: Norethindrone Acetate

Chemical name: 19-Norpregn-4-en-20-yn-3-one, 17-(acetyloxy)-, (17α)-

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

Structural Formula:



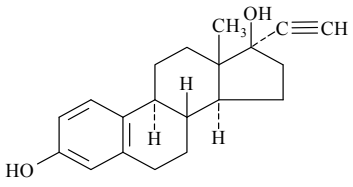
Physicochemical properties: A white solid with a melting point of 157° to 163°C, freely soluble in dioxane, sparingly soluble in ether, and insoluble in water

Proper name: Ethinyl estradiol

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

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 and femHRT Lo (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™/MPA).

Vasomotor Symptoms

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

A. Study 376-368

In Study 376-368, the effect of femHRT and femHRT Lo 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 Lo, femHRT, or placebo for a period of 16 weeks.

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

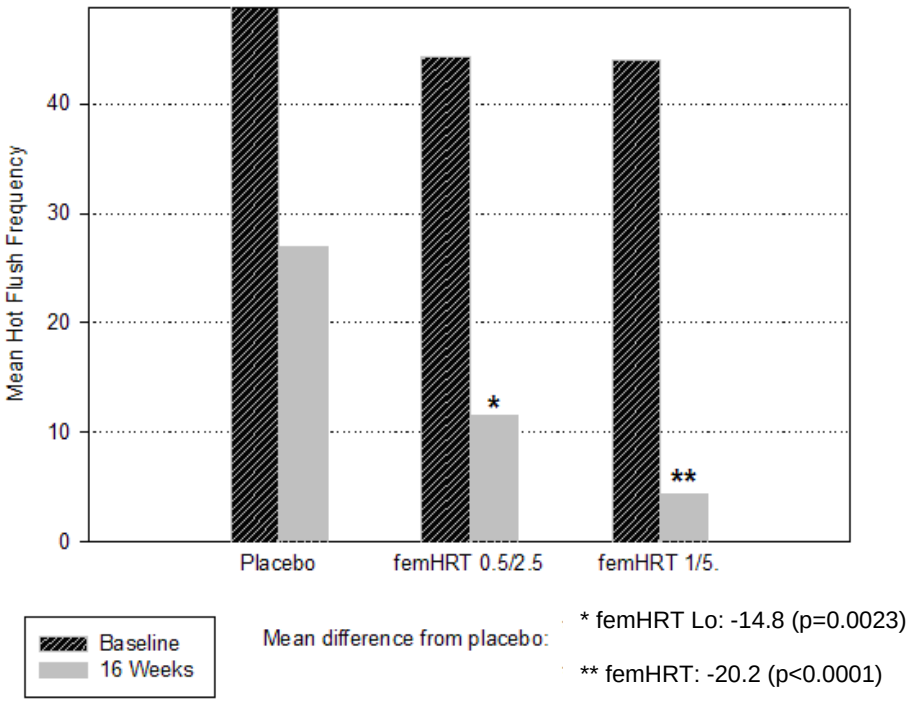


Figure 2. Reduction in Weekly Frequency of Hot Flushes: Mean Difference from Baseline for femHRT Lo, femHRT, and Placebo Groups at Week 16 (Study 376-368)

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 and femHRT Lo 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 was significantly greater than placebo from Weeks 3 and 5, for femHRT and femHRT Lo, respectively. Similarly, reduction in mean intensity of hot flushes was significantly greater than placebo from Weeks 3 and 6, for femHRT and femHRT Lo, respectively.

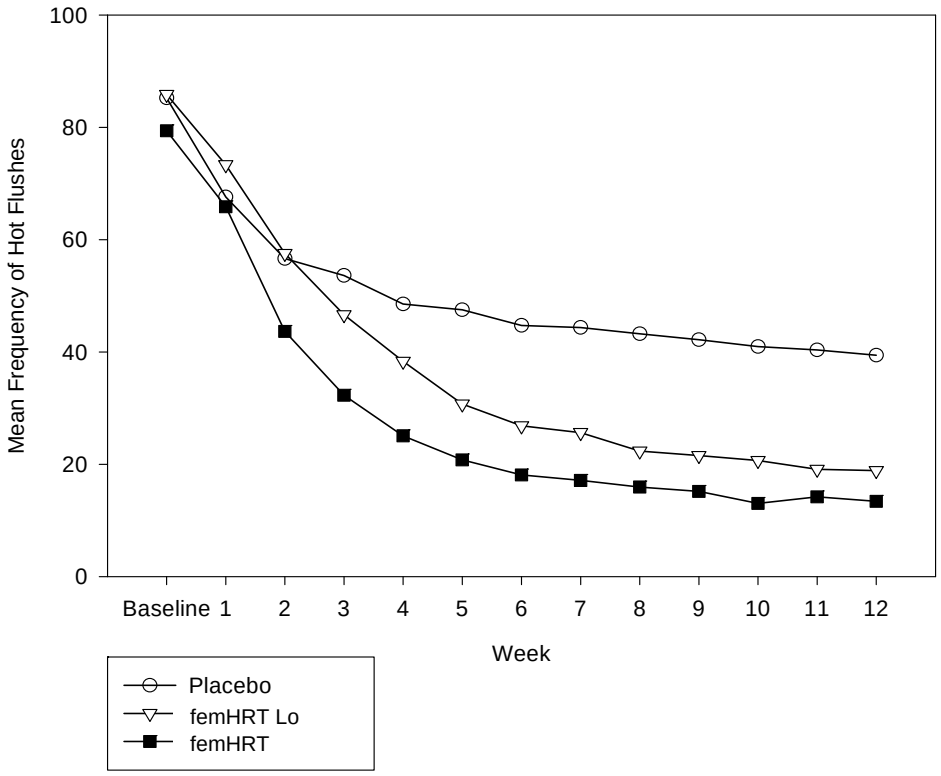


Figure 3. Mean Weekly Frequency of Hot Flushes by Treatment Group (Study 376-390)

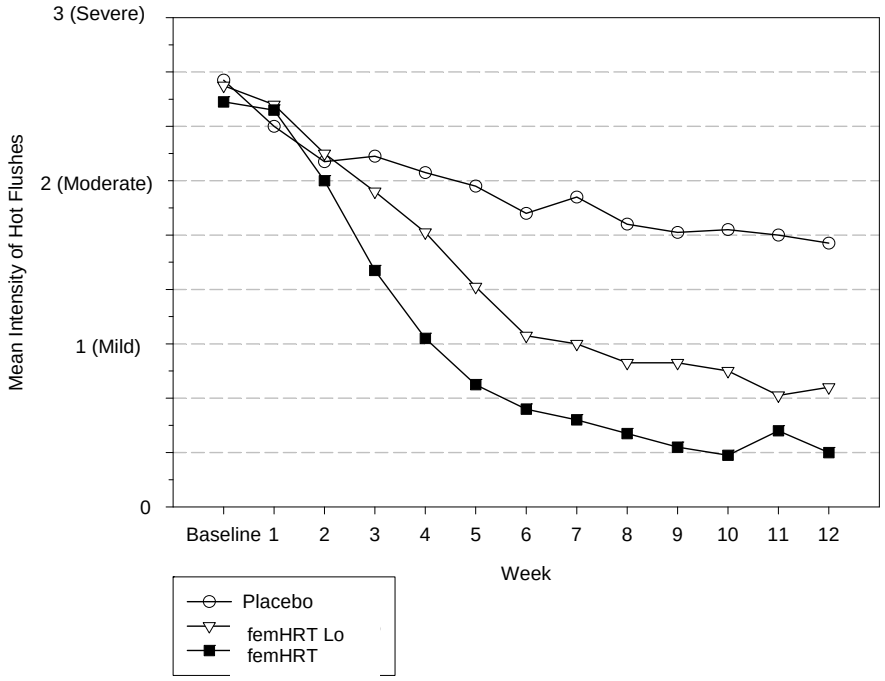


Figure 4. Mean Weekly Intensity of Hot Flushes by Treatment Group (Study 376-390)

Effect on Bone Mineral Density

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 Lo, femHRT, 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 Lo dose, while femHRT resulted in a significant increase in BMD at each annual assessment. The increase in BMD seen with femHRT 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 Lo and femHRT 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.

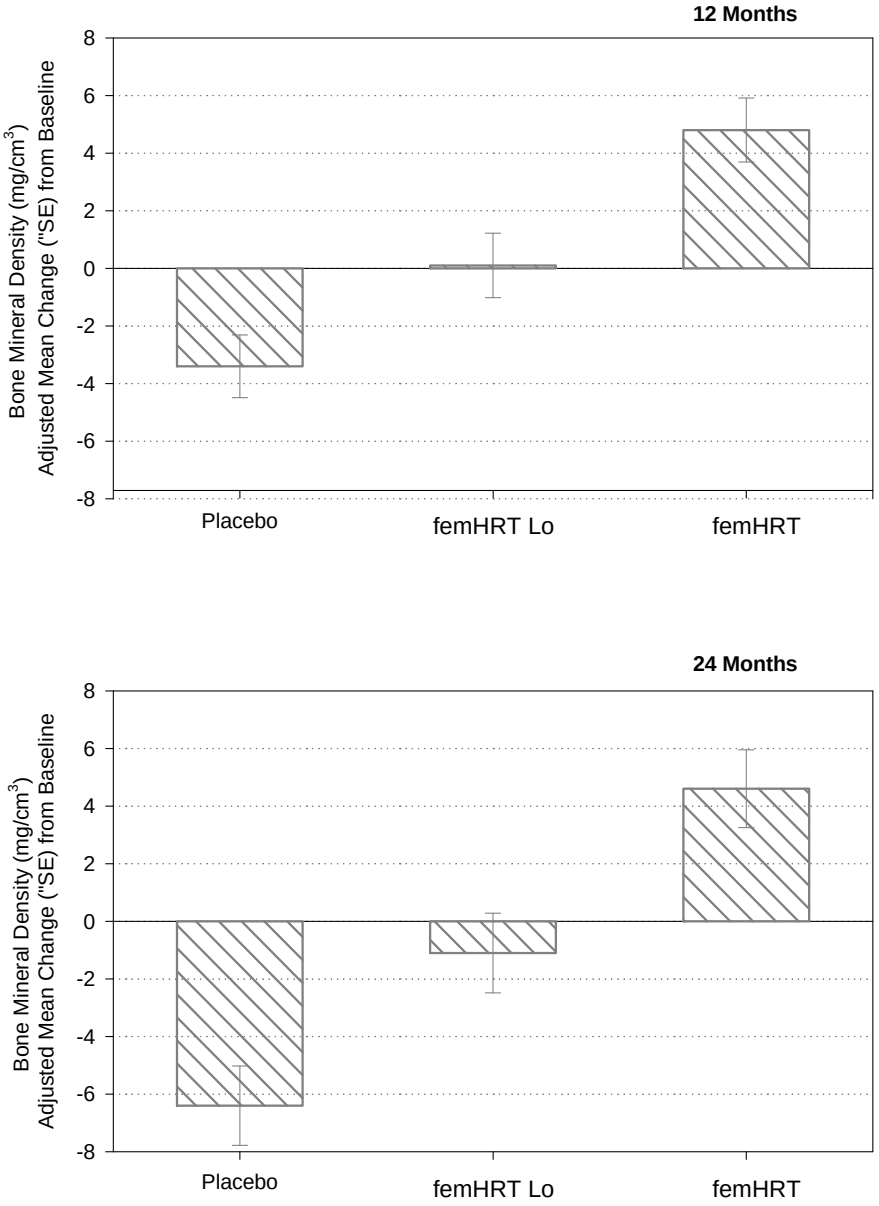


Figure 5. Bone Mineral Density (mg/cm^3) Adjusted Mean Change (± SE) for Baseline at Month 12 and Month 24 (CHART Study, 376-359)

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 the femHRT Lo or 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 Lo**	**femHRT**	**EE Alone**	
				2.5 µg	**5 µg**
Number of Patients Biopsied at Baseline	N = 134	N = 136	N = 143	N= 137	N = 139
Month 12 (% Patients)					
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[a]	0	0	0	0	1
Month 24 (% Patients)					
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[a]	1	0	0	1	2

[a]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, EE alone 5 µg, placebo, or 0.625 mg Premarin™/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. The additional experience from this comparative, controlled clinical trial provides further support for the protective endometrial effects of femHRT.

Bleeding and/or Spotting

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 and femHRT Lo patients reporting bleeding and/or spotting decreased steadily to 13% by end of the study.

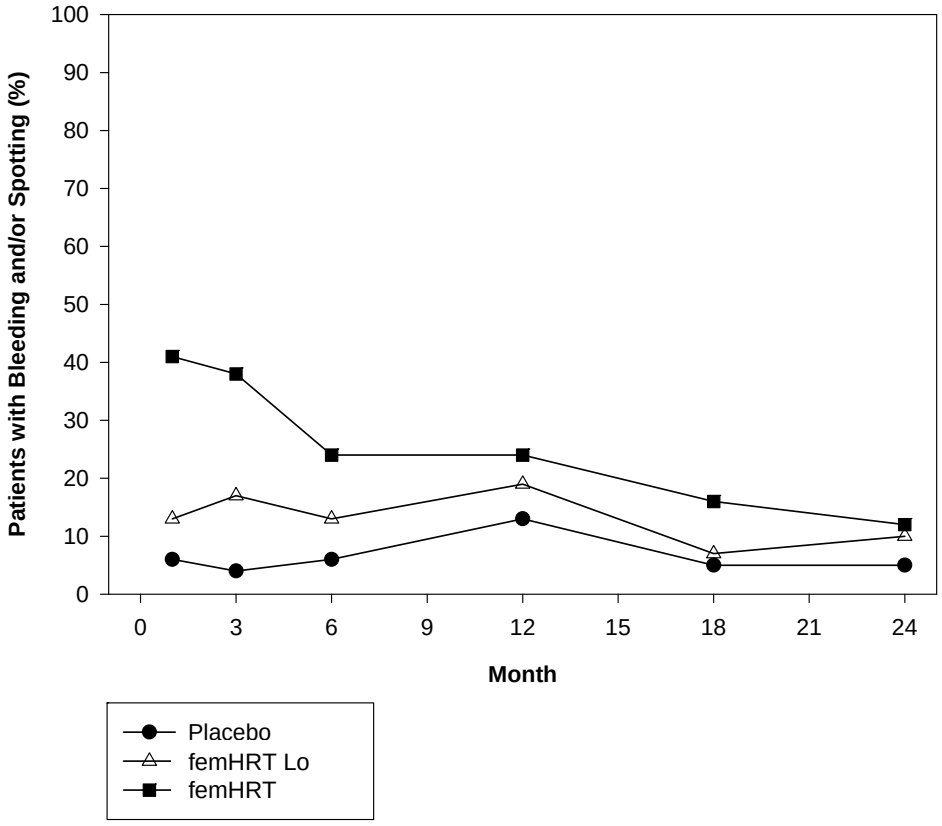


Figure 6: Incidence of Bleeding and/or Spotting with femHRT Lo, femHRT, and Placebo (*CHART Study* 376-359)

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.

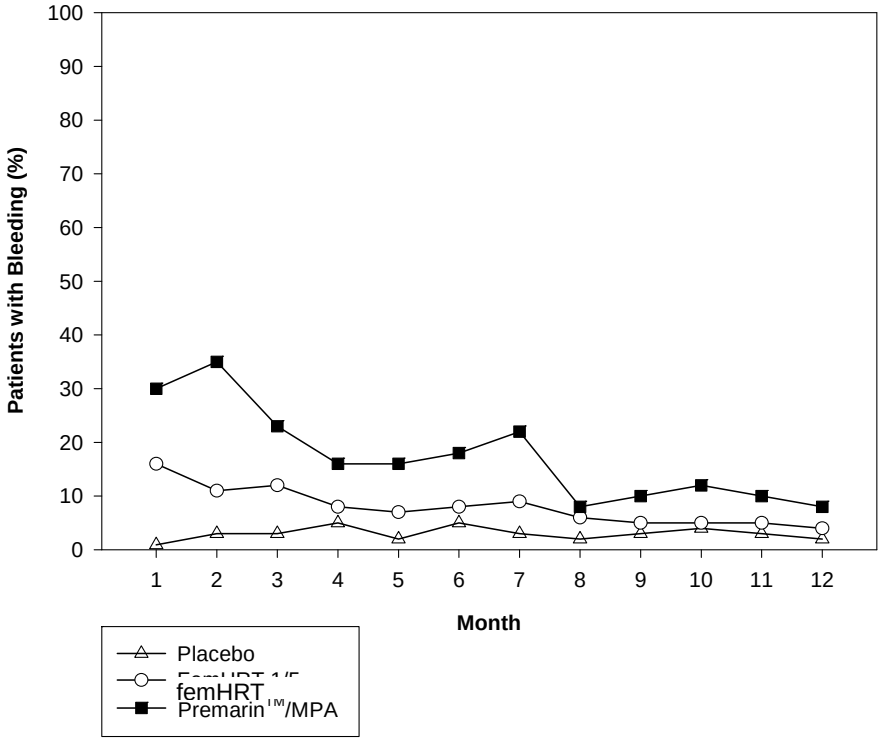


Figure 7: Monthly Incidence of Bleeding with femHRT, Placebo and Premarin^{TM}/MPA (Study 376-401, 12 Months)

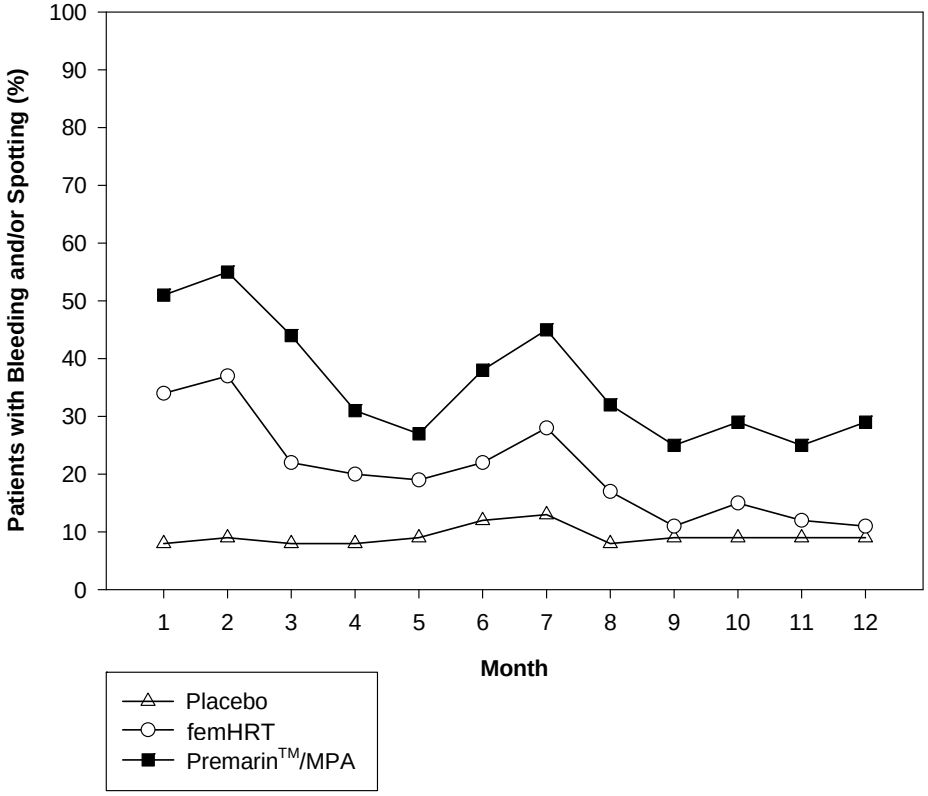


Figure 8. Monthly Incidence of Bleeding and/or Spotting with femHRT, Placebo and Premarin™/MPA (Study 376-401, 12 Months)

Cumulative Amenorrhea

Study 376-390

In Study 376-390, the rate of amenorrhea, defined as no bleeding or spotting, was evaluated for femHRT Lo, femHRT 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 Lo group (93%) and femHRT dose group (87%) were similar to that in the placebo group (Figure 9).

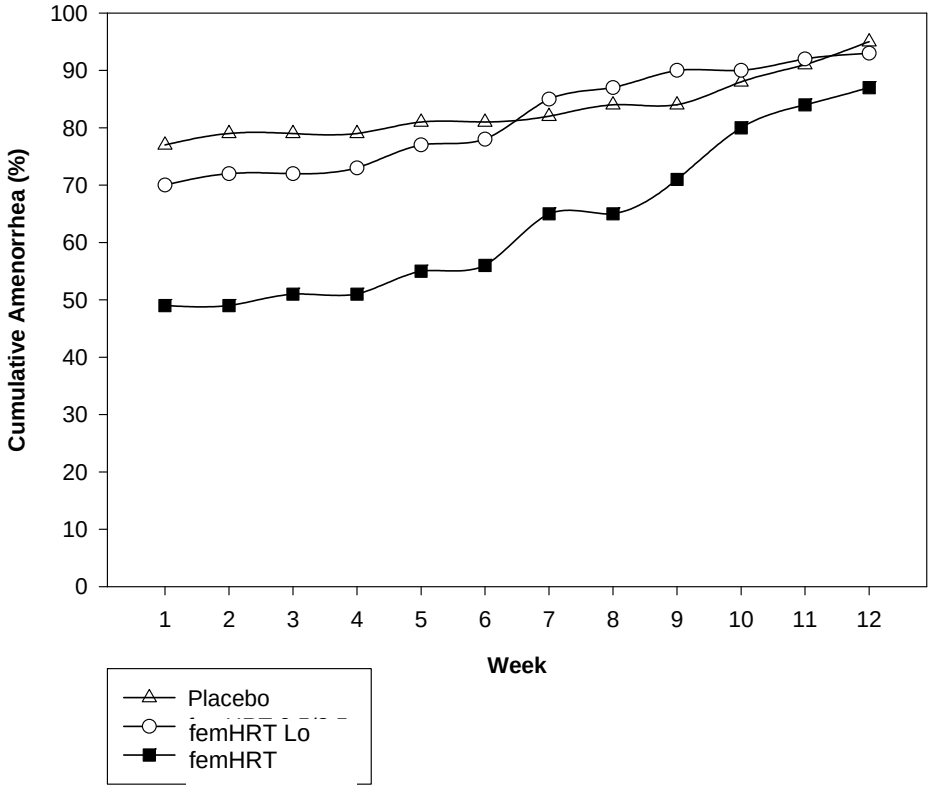


Figure 9. Percent of Patients with Cumulative Amenorrhea Over Time (Study 376-390)

CHART Study (376-359)
The cumulative incidence of amenorrhea was evaluated over 24 months for femHRT Lo, femHRT and placebo arms. Results are shown in Figure 10.

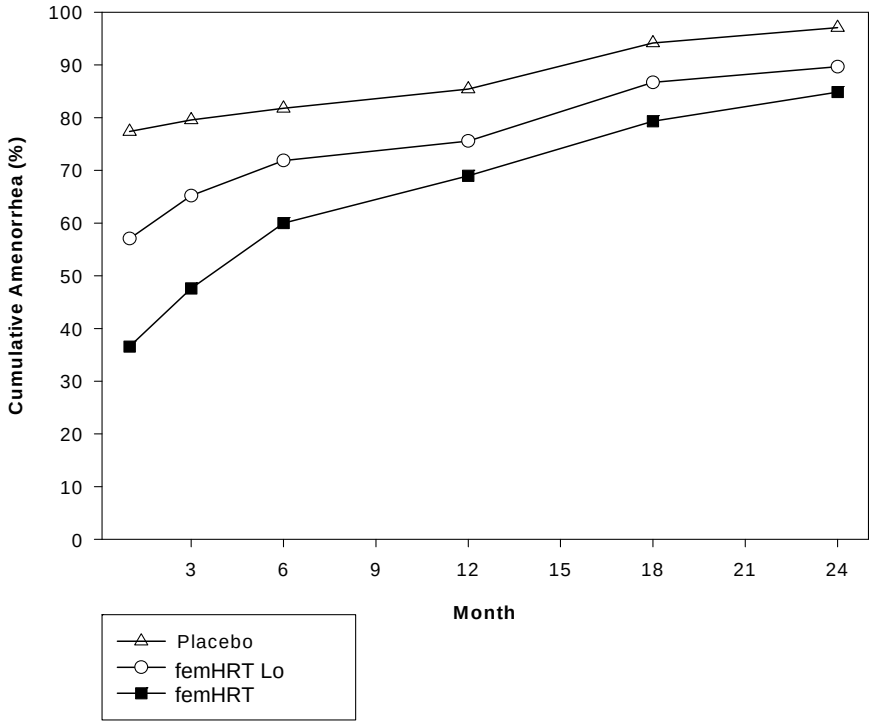


Figure 10. Patients with Cumulative Amenorrhea Over Time: Intent-To-Treat Population, Last Observation Carried Forward (*CHART Study*, 376-359)

Study 376-401

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

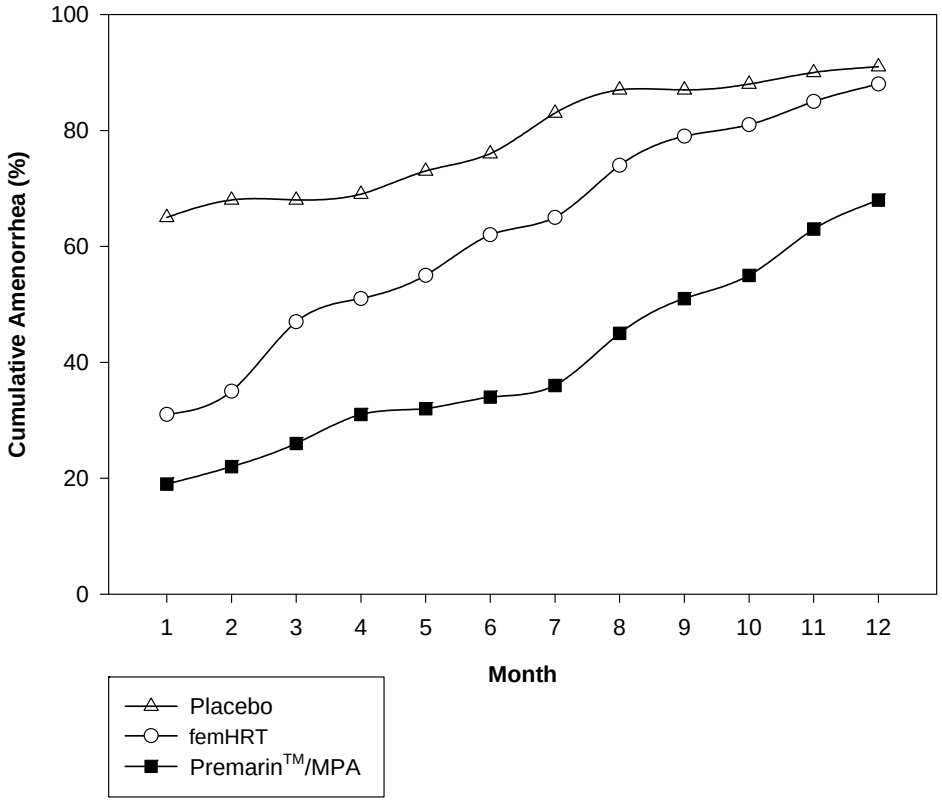


Figure 11. Patients With Cumulative Amenorrhea Over Time: Intent-To-Treat Population (Study 376-401)

Effects on Lipids

In the *CHART Study* (376-359), femHRT Lo and femHRT 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 Lo, 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		FemHRT (mg NA/μg EE)		Unopposed EE (μg EE)	
	Placebo	0.5/2.5 (Lo)	1/5	2.5	5
	N=129	N=128	N=132	N=126	N=128
Total Cholesterol[a]	1.6	-5.4	-7.0	0.9	2.3
HDL-C[a]	1.3	-0.1	-6.7	11.7	18.5
LDL-C	1.0	-8.0	-7.5	-5.9	-6.8
Triglycerides[a]	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 and femHRT Lo 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 and femHRT Lo 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 or femHRT Lo. 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

femHRT® Lo
0.5 mg Norethindrone Acetate and 2.5 µg Ethinyl Estradiol

femHRT®
1 mg Norethindrone Acetate and 5 µg Ethinyl Estradiol

This leaflet is part III of a three-part "Product Monograph" for femHRT® and femHRT® Lo and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about femHRT or femHRT Lo. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

- To relieve menopausal and postmenopausal symptoms such as hot flushes and night sweats
- To treat vulvar and vaginal atrophy due to lower estrogen levels related to menopause. Symptoms include itching. burning, dryness, and pain while having sex. If you use femHRT or femHRT Lo only to treat symptoms of vulvar and vaginal atrophy related to menopause, talk with your healthcare provider about whether a vaginal (topical) treatment might be better for you.
- To prevent thinning of the bones (osteoporosis). If you use femHRT or femHRT Lo only to prevent osteoporosis associate with menopause, talk to your healthcare provider about whether a different treatment or medicine without estrogen may be better for you. Weight-bearing exercise, like walking or running, cessation of smoking, adequate diet, 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.

femHRT and femHRT Lo should only be used in women with an intact uterus.

femHRT and femHRT Lo should be used only under the supervision of a doctor, with regular follow-up at least once a year to identify side effects associated with its use. Your first follow-up visit should be within 3 to 6 months of starting treatment. Your visit may include a blood pressure check, a breast exam, a Pap smear and pelvic exam. You should have a mammogram before starting treatment and at regular intervals as recommended by your doctor. Your doctor may recommend some blood tests.

You should carefully discuss the risks and benefits of hormone replacement therapy (HRT) with your doctor. You should regularly talk with your doctor about whether you still need treatment with HRT.

What it does
femHRT and femHRT Lo replace the estrogen in your body which decreases at menopause. Estrogen therapy can help to reduce your menopausal symptoms and to prevent thinning of bones related to menopause. The progestin hormone in femHRT and fernHRT Lo will help to reduce the risk of endometrial hyperplasia (stimulation of growth of the lining of the uterus). which could lead to cancer of the lining of the uterus (womb).

When it should not be used
You should not take femHRT or femHRT Lo:

- In the presence of liver disease
- 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 or femHRT Lo.
- If you have endometrial hyperplasia (overgrowth of the uterus lining)
- If you have undiagnosed or abnormal vaginal bleeding
- If you are pregnant or may be pregnant
- If you are breastfeeding
- 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
- 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 (estrogen) and norethindrone acetate (progestin)

What the non-medicinal ingredients are
femHRT and femHRT Lo tablets also contain calcium stearate, cornstarch, lactose monohydrate, and microcrystalline cellulose.

What dosage form it comes in
femHRT Lo 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 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

The Women's Health Initiative (WHI) trial is a large clinical study that assessed the benefits and risks of oral combined estrogen plus progestin therapy and oral estrogen-alone therapy compared with placebo (a pill with no active ingredients) in postmenopausal women.
The WHI trial indicated an increased risk of myocardial infarction (heart attack), stroke, breast cancer, pulmonary emboli (blood clots in the lungs) and deep vein thrombosis (blood clots in the large veins) in postmenopausal women taking oral combined estrogen plus progestin.
The WHI trial indicated an increased risk of stroke and deep vein thrombosis in postmenopausal women with prior hysterectomy (surgical removal of the uterus) taking oral estrogen-alone.
Therefore, you should highly consider the following:

- There is an increased risk of developing invasive breast cancer, heart attack, stroke and blood clots in both lungs and large veins with the use of estrogen plus progestin therapy.
- There is an increased risk of stroke and blood clots in the large veins with the use of estrogen-alone therapy.
- Estrogens with or without progestins should not be used for the prevention of heart disease or stroke.
- Estrogens with or without progestins should be used at the lowest effective dose and for the shortest period of time possible. Regular medical follow-up is advised.

- *Breast Cancer* – The results of the WHI trial indicated an increased risk of breast cancer in post-menopausal women taking combined estrogen plus progestin compared to women taking placebo. The results of the WHI trial indicated no difference in the risk of breast cancer in postmenopausal women with prior hysterectomy taking estrogen-alone compared to women taking placebo. Estrogens with or without progestins should not be taken by women who have a personal history of breast cancer. In addition, women with a family history of breast cancer or women with a history of breast lumps, breast biopsies or abnormal mammograms (breast x-rays) should consult with their doctor before starting HRT. Women should have a mammogram before starting HRT and at regular intervals during treatment as recommended by their doctor. Regular breast examinations by a doctor and regular breast self-examinations are recommended for all women. You should review technique for breast self-examination with your doctor.

  Overgrowth of the lining of the uterus and cancer of the uterus – The use of estrogen-alone therapy by post-menopausal women who still have a uterus increases the risk of developing endometrial hyperplasia (overgrowth of the lining of the uterus), which increases the risk of endometrial cancer (cancer of the lining of the uterus). The purpose of adding a progestin medication to estrogen therapy (as in femHRT and femHRT Lo) is to reduce the risk of endometrial hyperplasia..

- *Ovarian Cancer* – In some studies, the use of estrogen/progestin therapies for 5 or more years has been associated with an increased risk of ovarian cancer

- *Heart Disease and Stroke* – The results of the WHI trial indicated an increased risk of stroke and coronary heart disease in post-menopausal women taking combined estrogen plus progestin compared to women taking placebo. The results of the WHI trial indicated an increased risk of stroke, but no difference in the risk of coronary heart disease in post-menopausal women with prior hysterectomy taking estrogen alone compared to women taking placebo.

- *Abnormal blood clotting* – The results of the WHI trial indicated an increased risk of blood clots in the lungs and large veins in post-menopausal women taking combined estrogen plus progestin compared to women taking placebo. The results of the WHI trial indicated an increased risk of blood clots in the large veins, but no difference in the risk of blood clots in the lungs in post-menopausal women with prior hysterectomy taking estrogen-alone compared to women taking placebo.

  The risk of blood clots also increases with age, if you or a family member has had blood clots, if you smoke or if you are severely overweight. The risk of blood clots is also temporarily increased if you are immobilized for long periods of time and following major surgery. You should discuss risk factors for blood clots with your doctor since blood clots can be life-threatening or cause serious disability.

- *Gallbladder disease* – The use of estrogens by postmenopausal women has been associated with an increased risk of gallbladder disease requiring surgery.

- *Dementia* – The Women's Health Initiative Memory Study (WHIMS) was a substudy of the WHI trial and indicated an increased risk of dementia (loss of memory and intellectual function) in postmenopausal women age 65 and over taking oral combined estrogen plus progestin compared to women taking placebo.

  The WHIMS indicated no difference in the risk of dementia in post-menopausal women age 65 and over with prior hysterectomy taking oral estrogen-alone compared to women taking placebo.

BEFORE you use femHRT or femHRT Lo, talk to your doctor or pharmacist if you:

- have a history of allergy or intolerance to any medications or other substances
- have a personal history of breast disease (including breast lumps) and/or breast biopsies, or a family history of breast cancer
- have experienced any unusual or undiagnosed vaginal bleeding
- have a history of uterine fibroids or endometriosis
- have a history of liver disease, jaundice (yellowing of the eyes and/or skin) or itching related to estrogen use or during pregnancy
- have a history of migraine headache
- have a history of high blood pressure
- have a personal or family history of blood clots, or a personal history of heart disease or stroke
- have a history of kidney disease, asthma or epilepsy (seizures)
- have a history of bone disease (this includes certain metabolic conditions or cancers that can affect blood levels of calcium and phosphorus)
- have been diagnosed with diabetes
- have been diagnosed with porphyria (a disease of blood pigment)
- have a history of high cholesterol or high triglycerides
- are pregnant or may be pregnant
- have had a hysterectomy (surgical removal of the uterus)
- are breastfeeding
- have problems with your thyroid
- have been diagnosed with hearing loss due to otosclerosis
- have been told that you have a condition called hereditary hemangioma, or if you have had episodes of rapid swelling of the hands, feet, lips, eyes, tongue, throat (airway blockage) or digestive tract
- have been diagnosed with lupus
- smoke

INTERACTIONS WITH THIS MEDICATION

Some drugs may affect the activity of femHRT and femHRT Lo, 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.

PROPER USE OF THIS MEDICATION

Usual Dose

femHRT and femHRT Lo must only be taken under the supervision of your doctor. femHRT and femHRT Lo are each very simple to take – one pill by mouth, once a day, every day. You can take femHRT or femHRT Lo 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, even if there are no symptoms.

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.

HOW TO STORE IT

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

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The following side effects have been reported with femHRT or femHRT Lo 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 (cramps, bloating)
- Dyspepsia
- Diarrhea
- Nervousness
- Urinary Tract Infection

IMPORTANT SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM		
Symptom / Effect	**Talk with your doctor or pharmacist**	**Stop taking drug and call your doctor or pharmacist**
Severe or persistent nausea, vomiting and tenderness in the abdomen	✓	
Lump in the breast	✓	
Crushing chest pain or chest heaviness		✓
Pain, or swollen veins, i.e., varicose veins		✓
Pain, tenderness, swelling, or redness in the leg		✓
Persistent sad mood		✓
Sharp pain in the chest, coughing blood or sudden shortness of breath		✓
Sudden partial or complete loss of vision		✓
Sudden severe headache or worsening of headache, vomiting, dizziness, fainting, disturbance of vision or speech or weakness or numbness in an arm or a leg		✓
Unexpected vaginal bleeding	✓	
Yellowing of the skin or eyes (jaundice)		✓

This is not a complete list of side effects. For any unexpected effects while taking femHRT or femHRT Lo, contact your doctor or pharmacist. For more information, talk to your healthcare provider.

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 or femHRT Lo. This is normal and occurs because the endometrium (lining of the uterus) is adjusting to the hormones. With femHRT and femHRT Lo, bleeding normally stops during the first 3 to 6 months of therapy. If you experience vaginal bleeding while taking femHRT or femHRT Lo, 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 or femHRT Lo?
In clinical studies, women on femHRT or femHRT Lo did not gain any more weight than women who were not on femHRT or femHRT Lo.

MORE INFORMATION

REPORTING SUSPECTED SIDE EFFECTS

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

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

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

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

This document plus the full product monograph, prepared for health professionals is available by contacting Warner Chilcott Canada Co. at: 1-800-565-0814.

This leaflet was prepared by Warner Chilcott Canada Co.
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