

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use FYAVOLV safely and effectively. See full prescribing information for FYAVOLV.

Fyavolv™ (norethindrone acetate and ethinyl estradiol tablets USP), for oral use

Initial U.S. Approval: 1968

### **WARNING: CARDIOVASCULAR DISORDERS, BREAST CANCER, ENDOMETRIAL CANCER AND PROBABLE DEMENTIA**

*See full prescribing information for complete boxed warning.*

#### **Estrogen Plus Progestin Therapy**

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

#### **Estrogen-Alone Therapy**

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

#### **-----RECENT MAJOR CHANGES-----**

Contraindications (4)	1/2014
Warnings and Precautions, Hereditary Angioedema (5.15)	1/2014

#### **-----INDICATIONS AND USAGE-----**

Fyavolv is an estrogen plus progestin indicated in a woman with a uterus for:

- Treatment of Moderate to Severe Vasomotor Symptoms due to Menopause (1.1)
- Prevention of Postmenopausal Osteoporosis (1.2)

#### **-----DOSAGE AND ADMINISTRATION-----**

- One tablet taken orally once daily (2.1, 2.2)

#### **-----DOSAGE FORMS AND STRENGTHS-----**

- Round shaped, white to off-white tablet contains 0.5 mg norethindrone acetate and 0.0025 mg ethinyl estradiol (3)
- Round shaped, blue tablet contains 1 mg norethindrone acetate and 0.005 mg ethinyl estradiol (3)

#### **-----CONTRAINDICATIONS-----**

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

#### **-----WARNINGS AND PRECAUTIONS-----**

- Estrogens increase the risk of gallbladder disease (5.4)
- Discontinue estrogen if severe hypercalcemia, loss of vision, severe hypertriglyceridemia or cholestatic jaundice occurs (5.5, 5.6, 5.9, 5.10)
- Monitor thyroid function in women on thyroid replacement therapy (5.11, 5.18)

#### **-----ADVERSE REACTIONS-----**

Most common adverse reactions (incidence greater than or equal to 5 percent) are headache, abdominal pain, breast pain, and edema (generalized). (6.1)

**To report SUSPECTED ADVERSE REACTIONS, contact Lupin Pharmaceuticals, Inc. at 1-800-399-2561, or FDA at 1-800-FDA-1088 or [www.fda.gov/Medwatch](http://www.fda.gov/Medwatch).**

#### **-----DRUG INTERACTIONS-----**

- Inducers and/or inhibitors of CYP3A4 may affect estrogen drug metabolism (7.1)

#### **-----USE IN SPECIFIC POPULATIONS-----**

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

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

Revised: 9/2015

---

**FULL PRESCRIBING INFORMATION: CONTENTS\***  
**WARNING: CARDIOVASCULAR DISORDERS, BREAST**  
**CANCER, ENDOMETRIAL CANCER AND PROBABLE**  
**DEMENTIA**

- 1. INDICATIONS AND USAGE**
  - 1.1. Treatment of Moderate to Severe Vasomotor Symptoms due to Menopause
  - 1.2. Prevention of Postmenopausal Osteoporosis
- 2. DOSAGE AND ADMINISTRATION**
  - 2.1. Treatment of Moderate to Severe Vasomotor Symptoms due to Menopause
  - 2.2. Prevention of Postmenopausal Osteoporosis
- 3. DOSAGE FORMS AND STRENGTHS**
- 4. CONTRAINDICATIONS**
- 5. WARNINGS AND PRECAUTIONS**
  - 5.1. Cardiovascular Disorders
  - 5.2. Malignant Neoplasms
  - 5.3. Probable Dementia
  - 5.4. Gallbladder Disease
  - 5.5. Hypercalcemia
  - 5.6. Visual Abnormalities
  - 5.7. Addition of a Progestin When a Woman Has Not Had a Hysterectomy
  - 5.8. Elevated Blood Pressure
  - 5.9. Hypertriglyceridemia
  - 5.10. Hepatic Impairment and/or Past History of Cholestatic Jaundice
  - 5.11. Hypothyroidism
  - 5.12. Fluid Retention
  - 5.13. Hypocalcemia
  - 5.14. Exacerbation of Endometriosis
  - 5.15. Hereditary Angioedema
  - 5.16. Exacerbation of Other Conditions
  - 5.17. Laboratory Tests
  - 5.18. Drug-Laboratory Test Interactions
- 6. ADVERSE REACTIONS**
  - 6.1. Clinical Trials Experience
  - 6.2. Postmarketing Experience
- 7. DRUG INTERACTIONS**
  - 7.1. Effect of Other Drugs on Combined Hormonal Products
  - 7.2. Effect of Combined Hormonal Products on Other Drugs

- 8. USE IN SPECIFIC POPULATIONS**
  - 8.1. Pregnancy
  - 8.3. Nursing Mothers
  - 8.4. Pediatric Use
  - 8.5. Geriatric Use
  - 8.6. Renal Impairment
  - 8.7. Hepatic Impairment
- 10. OVERDOSAGE**
- 11. DESCRIPTION**
- 12. CLINICAL PHARMACOLOGY**
  - 12.1. Mechanism of Action
  - 12.2. Pharmacodynamics
  - 12.3. Pharmacokinetics
- 13. NONCLINICAL TOXICOLOGY**
  - 13.1. Carcinogenesis, Mutagenesis, Impairment of Fertility
- 14. CLINICAL STUDIES**
  - 14.1. Effects on Vasomotor Symptoms
  - 14.2. Effects on the Endometrium
  - 14.3. Effects on Uterine Bleeding or Spotting
  - 14.4. Effect on Bone Mineral Density
  - 14.5. Women's Health Initiative Studies
  - 14.6. Women's Health Initiative Memory Study
- 15. REFERENCES**
- 16. HOW SUPPLIED/STORAGE AND HANDLING**
  - 16.1. How Supplied
  - 16.2. Storage and Handling
- 17. PATIENT COUNSELING INFORMATION**
  - 17.1. Abnormal Vaginal Bleeding
  - 17.2. Possible Serious Adverse Reactions with Estrogen Plus Progestin Therapy
  - 17.3. Possible Less Serious but Common Adverse Reactions with Estrogen Plus Progestin Therapy

\* Sections or subsections omitted from the Full Prescribing Information are not listed.

## FULL PRESCRIBING INFORMATION

### **WARNING: CARDIOVASCULAR DISORDERS, BREAST CANCER, ENDOMETRIAL CANCER AND PROBABLE DEMENTIA**

#### **Estrogen Plus Progestin Therapy**

##### **Cardiovascular Disorders and Probable Dementia**

Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia [see *WARNINGS AND PRECAUTIONS* (5.1, 5.3), and *CLINICAL STUDIES* (14.5, 14.6)].

The Women's Health Initiative (WHI) estrogen plus progestin substudy reported an increased risk of deep vein thrombosis (DVT), pulmonary embolism (PE), stroke and myocardial infarction (MI) in postmenopausal women (50 to 79 years of age) during 5.6 years of treatment with daily oral conjugated estrogens (CE) [0.625 mg] combined with medroxyprogesterone acetate (MPA) [2.5 mg], relative to placebo [see *WARNINGS AND PRECAUTIONS* (5.1), and *CLINICAL STUDIES* (14.5)].

The WHI Memory Study (WHIMS) estrogen plus progestin ancillary study of the WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with daily CE (0.625 mg) combined with MPA (2.5 mg), relative to placebo. It is unknown whether this finding applies to younger postmenopausal women [see *WARNINGS AND PRECAUTIONS* (5.3), *USE IN SPECIFIC POPULATIONS* (8.5), and *CLINICAL STUDIES* (14.6)].

##### **Breast Cancer**

The WHI estrogen plus progestin substudy also demonstrated an increased risk of invasive breast cancer [see *WARNINGS AND PRECAUTIONS* (5.2), and *CLINICAL STUDIES* (14.5)].

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

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

#### **Estrogen-Alone Therapy**

##### **Endometrial Cancer**

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

undiagnosed persistent or recurring abnormal genital bleeding [see **WARNINGS AND PRECAUTIONS** (5.2)].

#### **Cardiovascular Disorders and Probable Dementia**

Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia [see **WARNINGS AND PRECAUTIONS** (5.1, 5.3), and **CLINICAL STUDIES** (14.5, 14.6)].

The WHI estrogen-alone substudy reported increased risks of stroke and DVT in postmenopausal women (50 to 79 years of age) during 7.1 years of treatment with daily oral CE (0.625 mg)-alone, relative to placebo [see **WARNINGS AND PRECAUTIONS** (5.1), and **CLINICAL STUDIES** (14.5)].

The WHIMS estrogen-alone ancillary study of the WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 5.2 years of treatment with daily CE (0.625 mg)-alone, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women [see **WARNINGS AND PRECAUTIONS** (5.3), **USE IN SPECIFIC POPULATIONS** (8.5), and **CLINICAL STUDIES** (14.6)].

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

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

## **1 INDICATIONS AND USAGE**

### **1.1 Treatment of Moderate to Severe Vasomotor Symptoms due to Menopause**

### **1.2 Prevention of Postmenopausal Osteoporosis**

#### *Limitation of Use*

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

## **2 DOSAGE AND ADMINISTRATION**

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

### **2.1 Treatment of Moderate to Severe Vasomotor Symptoms due to Menopause**

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

### **2.2 Prevention of Postmenopausal Osteoporosis**

Fyavolv therapy consists of a single tablet taken orally once daily.

### 3 DOSAGE FORMS AND STRENGTHS

The following two strengths of Fyavolv tablets are available:

Fyavolv (0.5 mg/0.0025 mg): Each white to off-white, round film-coated tablet, debossed with “F51” on one side and “LU” on the other side contains 0.5 mg norethindrone acetate and 0.0025 mg ethinyl estradiol.

Fyavolv (1 mg/0.005 mg): Each blue, round film-coated tablet, debossed with “F52” on one side and “LU” on the other side contains 1 mg norethindrone acetate and 0.005 mg ethinyl estradiol.

### 4 CONTRAINDICATIONS

Fyavolv is contraindicated in women with any of the following conditions:

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

### 5 WARNINGS AND PRECAUTIONS

#### 5.1 Cardiovascular Disorders

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

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

#### *Stroke*

In the WHI estrogen plus progestin substudy, a statistically significant increased risk of stroke was reported in women 50 to 79 years of age receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women in the same age group receiving placebo (33 versus 25 per 10,000 women-years) [see *CLINICAL STUDIES (14.5)*]. The increase in risk was demonstrated after the first year and persisted.<sup>1</sup> Should a stroke occur or be suspected, estrogen plus progestin therapy should be discontinued immediately.

In the WHI estrogen-alone substudy, a statistically significant increased risk of stroke was reported in women 50 to 79 years of age receiving daily conjugated estrogens CE (0.625 mg)-alone compared to women in the same age group receiving placebo (45 versus 33 per 10,000

women-years). The increase in risk was demonstrated in year 1 and persisted [see *CLINICAL STUDIES (14.5)*]. Should a stroke occur or be suspected, estrogen-alone therapy should be discontinued immediately.

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

### ***Coronary Heart Disease***

In the WHI estrogen plus progestin substudy, there was a statistically non-significant increased risk of coronary heart disease (CHD) events (defined as nonfatal MI, silent MI, or CHD death) reported in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women receiving placebo (41 versus 34 per 10,000 women-years).<sup>1</sup> An increase in relative risk was demonstrated in year 1, and a trend toward decreasing relative risk was reported in years 2 through 5 [see *CLINICAL STUDIES (14.5)*].

In the WHI estrogen-alone substudy, no overall effect on CHD events was reported in women receiving estrogen-alone compared to placebo<sup>2</sup> [see *CLINICAL STUDIES (14.5)*].

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

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

### ***Venous Thromboembolism***

In the WHI estrogen plus progestin substudy, a statistically significant 2-fold greater rate of VTE (DVT and PE) was reported in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women receiving placebo (35 versus 17 per 10,000 women-years). Statistically significant increases in risk for both DVT (26 versus 13 per 10,000 women-years) and PE (18 versus 8 per 10,000 women-years) were also demonstrated. The increase in VTE risk was demonstrated during the first year and persisted<sup>3</sup> [see *CLINICAL STUDIES (14.5)*]. Should a VTE occur or be suspected, estrogen plus progestin therapy should be discontinued immediately.

In the WHI estrogen-alone substudy, the risk of VTE was increased for women receiving daily CE (0.625 mg) alone compared to placebo (30 versus 22 per 10,000 women-years), although

only the increased risk of DVT reached statistical significance (23 versus 15 per 10,000 women-years). The increase in VTE risk was demonstrated during the first 2 years<sup>4</sup> [see *CLINICAL STUDIES (14.5)*]. Should a VTE occur or be suspected, estrogen-alone therapy should be discontinued immediately.

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

## **5.2 Malignant Neoplasms**

### ***Breast Cancer***

The most important randomized clinical trial providing information about breast cancer in estrogen plus progestin users is the WHI substudy of daily CE (0.625 mg) plus MPA (2.5 mg). After a mean follow-up of 5.6 years, the estrogen plus progestin substudy reported an increased risk of invasive breast cancer in women who took daily CE plus MPA. In this substudy, prior use of estrogen-alone or estrogen plus progestin therapy was reported by 26 percent of the women. The relative risk of invasive breast cancer was 1.24, and the absolute risk was 41 versus 33 cases per 10,000 women-years for CE plus MPA compared with placebo [see *CLINICAL STUDIES (14.5)*]. Among women who reported prior use of hormone therapy, the relative risk of invasive breast cancer was 1.86 and the absolute risk was 46 versus 25 cases per 10,000 women-years for CE plus MPA compared with placebo. Among women who reported no prior use of hormone therapy, the relative risk of invasive breast cancer was 1.09, and the absolute risk was 40 versus 36 cases per 10,000 women-years for CE plus MPA compared with placebo. In the same substudy, invasive breast cancers were larger, were more likely to be node positive, and were diagnosed at a more advanced stage in the CE (0.625 mg) plus MPA (2.5 mg) group compared with the placebo group. Metastatic disease was rare with no apparent difference between the two groups. Other prognostic factors, such as histologic subtype, grade and hormone receptor status did not differ between the groups<sup>5</sup> [see *CLINICAL STUDIES (14.5)*].

The most important randomized clinical trial providing information about breast cancer in estrogen-alone users is the WHI substudy of daily CE (0.625 mg)-alone. In the WHI estrogen-alone substudy, after an average follow up of 7.1 years, daily CE-alone was not associated with an increased risk of invasive breast cancer (relative risk [RR] 0.80 [see *CLINICAL STUDIES (14.5)*]).

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

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

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

### ***Endometrial Cancer***

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

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

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

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

### ***Ovarian Cancer***

The WHI estrogen plus progestin substudy reported a statistically non-significant increased risk of ovarian cancer. After an average follow-up of 5.6 years, the relative risk for ovarian cancer for CE plus MPA versus placebo was 1.58 (95 percent CI, 0.77 to 3.24). The absolute risk for CE plus MPA versus placebo was 4 versus 3 cases per 10,000 women-years<sup>7</sup>. In some epidemiologic studies, the use of estrogen plus progestin and estrogen-only products, in particular for 5 or more years, has been associated with an increased risk of ovarian cancer. However, the duration of exposure associated with increased risk is not consistent across all epidemiologic studies and some report no association.

### **5.3 Probable Dementia**

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

After an average follow-up of 4 years, 40 women in the CE plus MPA group and 21 women in the placebo group were diagnosed with probable dementia. The relative risk of probable

dementia for CE plus MPA versus placebo was 2.05 (95 percent CI, 1.21 to 3.48). The absolute risk of probable dementia for CE plus MPA versus placebo was 45 versus 22 cases per 10,000 women-years<sup>8</sup> [see *USE IN SPECIFIC POPULATIONS* (8.5), and *CLINICAL STUDIES* (14.6)].

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

After an average follow-up of 5.2 years, 28 women in the estrogen-alone group and 19 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE-alone versus placebo was 1.49 (95 percent CI, 0.83 to 2.66). The absolute risk of probable dementia for CE-alone versus placebo was 37 versus 25 cases per 10,000 women-years<sup>8</sup> [see *USE IN SPECIFIC POPULATION* (8.5), and *CLINICAL STUDIES* (14.6)].

When data from the two populations in the WHIMS estrogen-alone and estrogen plus progestin ancillary studies were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.76 (95 percent CI, 1.19 to 2.60). Since both ancillary substudies were conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women<sup>8</sup> [see *USE IN SPECIFIC POPULATION* (8.5), and *CLINICAL STUDIES* (14.6)].

#### **5.4 Gallbladder Disease**

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

#### **5.5 Hypercalcemia**

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

#### **5.6 Visual Abnormalities**

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

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

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

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

### **5.8 Elevated Blood Pressure**

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

### **5.9 Hypertriglyceridemia**

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

### **5.10 Hepatic Impairment and/or a Past History of Cholestatic Jaundice**

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

### **5.11 Hypothyroidism**

Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Women with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T<sub>4</sub> and T<sub>3</sub> serum concentrations in the normal range. Women dependent on thyroid hormone replacement therapy who are also receiving estrogen may require increased doses of their thyroid replacement therapy. These women should have their thyroid function monitored in order to maintain their free thyroid hormone levels in an acceptable range.

### **5.12 Fluid Retention**

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

### **5.13 Hypocalcemia**

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

### **5.14 Exacerbation of Endometriosis**

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

### **5.15 Hereditary Angioedema**

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

### **5.16 Exacerbation of Other Conditions**

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

### 5.17 Laboratory Tests

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

### 5.18 Drug-Laboratory Test Interactions

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

Increased TBG levels leading to increased circulating total thyroid hormone levels as measured by protein-bound iodine (PBI), T<sub>4</sub> levels (by column or by radioimmunoassay) or T<sub>3</sub> levels by radioimmunoassay. T<sub>3</sub> resin uptake is decreased, reflecting the elevated TBG. Free T<sub>4</sub> and free T<sub>3</sub> concentrations are unaltered. Women on thyroid replacement therapy may require higher doses of thyroid hormone.

Other binding proteins may be elevated in serum, for example, corticosteroid binding globulin (CBG), sex hormone-binding globulin (SHBG), leading to increased total circulating corticosteroids and sex steroids, respectively. Fyavolv 1/5 was associated with an SHBG increase of 22 percent. Free hormone concentrations, such as testosterone and estradiol, may be decreased. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).

Increased plasma high-density lipoprotein (HDL) and HDL<sub>2</sub> cholesterol subfraction concentrations, reduced low-density lipoprotein (LDL) cholesterol concentration, increased triglycerides levels.

Impaired glucose tolerance.

## 6 ADVERSE REACTIONS

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

- Cardiovascular Disorders [*see BOXED WARNING, WARNINGS AND PRECAUTIONS (5.1)*].
- Malignant Neoplasms [*see BOXED WARNING, WARNINGS AND PRECAUTIONS (5.2)*].

### 6.1 Clinical Trials Experience

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

Adverse reactions reported by  $\geq 5$  percent of subjects in controlled clinical studies of norethindrone acetate and ethinyl estradiol are shown in [Table 1](#).

**Table 1. Associated Adverse Reactions Reported by ≥5 Percent of Subjects by Body System<sup>a</sup>**

BODY SYSTEM/ Adverse Reaction	Number (Percent) of Subjects		
	Placebo N = 247	Norethindrone Acetate and Ethinyl Estradiol 0.5/2.5 N = 244	Norethindrone Acetate and Ethinyl Estradiol 1/5 N = 258
BODY AS A WHOLE	23 (12.8)	30 (16.9)	30 (15.7)
Edema – Generalized	10 (4.0)	12 (4.9)	11 (4.3)
Headache	12 (4.9)	14 (5.7)	16 (6.2)
DIGESTIVE SYSTEM	8 (4.4)	17 (9.6)	25 (13.1)
Abdominal Pain	3 (1.2)	13 (5.3)	14 (6.8)
UROGENITAL SYSTEM	20 (11.1)	34 (19.2)	45 (23.6)
Breast Pain	9 (3.6)	22 (9.0)	20 (7.8)

<sup>a</sup> The total number of subjects for each body system may be less than the number of subjects with AEs in that body system because a subject may have had more than one AE per body system

## 6.2 Postmarketing Experience

The following additional adverse reactions have been identified during post-approval use of norethindrone acetate and ethinyl estradiol. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

### *Genitourinary System*

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

### *Breasts*

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

### *Cardiovascular*

Deep and superficial venous thrombosis; pulmonary embolism; thrombophlebitis; thrombosis; chest pain; myocardial infarction; cerebrovascular accident (stroke); transient ischemic attack; hemiparesis; increase in blood pressure; irregular heart rate; palpitations; dyspnea.

### *Gastrointestinal*

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

### *Skin*

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

## **Eyes**

Retinal vascular thrombosis; visual impairment; intolerance to contact lenses.

## **Central Nervous System (CNS)**

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

## **Miscellaneous**

Increase or decrease in weight; reduced carbohydrate tolerance; aggravation of porphyria; edema; arthralgias; leg cramps; back pain; changes in libido; urticaria, angioedema, anaphylactoid/anaphylactic reactions; hypocalcemia; exacerbation of asthma; increased triglycerides; blood glucose abnormal; fatigue; myalgia; hypersensitivity.

## **7 DRUG INTERACTIONS**

No drug-drug interaction studies have been conducted for norethindrone acetate and ethinyl estradiol.

### **7.1 Effect of Other Drugs on Combined Hormonal Products**

#### ***Substances decreasing or increasing the plasma concentration of estrogen***

*In vitro* and *in vivo* studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4 such as St. John's wort (*Hypericum perforatum*) preparations, phenobarbital, carbamazepine and rifampin may decrease the plasma concentration of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4 such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice may increase the plasma concentration of estrogens and may result in side effects. Co-administration of atorvastatin and certain hormonal products containing ethinyl estradiol increase AUC values for ethinyl estradiol approximately 20 percent. Ascorbic acid and acetaminophen may increase the plasma ethinyl estradiol concentration, possibly by inhibition of conjugation.

### **7.2 Effect of Combined Hormonal Products on Other Drugs**

Combination hormonal products containing some synthetic estrogens (for example, ethinyl estradiol) may inhibit the metabolism of other compounds. Combination hormonal products have been shown to significantly decrease the plasma concentration of lamotrigine likely due to induction of lamotrigine glucuronidation. This may reduce seizure control; therefore, dosage adjustments of lamotrigine may be necessary.

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

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

### **8.3 Nursing Mothers**

Norethindrone acetate and ethinyl estradiol should not be used during lactation. Estrogen administration to nursing women has been shown to decrease the quantity and quality of the breast milk. Detectable amounts of estrogen and progestin have been identified in the breast milk of women receiving estrogen plus progestin therapy. Caution should be exercised when norethindrone acetate and ethinyl estradiol is administered to a nursing woman.

### **8.4 Pediatric Use**

Norethindrone acetate and ethinyl estradiol is not indicated in children. Clinical studies have not been conducted in the pediatric population.

### **8.5 Geriatric Use**

There have not been sufficient numbers of geriatric women involved in clinical studies utilizing norethindrone acetate and ethinyl estradiol to determine whether those over 65 years of age differ from younger subjects in their response to norethindrone acetate and ethinyl estradiol.

#### ***The Women's Health Initiative Studies***

In the WHI estrogen plus progestin substudy (daily CE [0.625 mg] plus MPA [2.5 mg] versus placebo), there was a higher relative risk of nonfatal stroke and invasive breast cancer in women greater than 65 years of age [*see CLINICAL STUDIES (14.5)*].

In the WHI estrogen-alone substudy (daily CE [0.625 mg]-alone versus placebo), there was a higher relative risk of stroke in women greater than 65 years of age [*see CLINICAL STUDIES (14.5)*].

#### ***The Women's Health Initiative Memory Study***

In the WHIMS ancillary studies of postmenopausal women 65 to 79 years of age, there was an increased risk of developing probable dementia in women receiving estrogen plus progestin or estrogen-alone when compared to placebo [*see WARNINGS AND PRECAUTIONS (5.3), and CLINICAL STUDIES (14.6)*].

Since both ancillary studies were conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women<sup>8</sup> [*see WARNINGS AND PRECAUTIONS (5.3), and CLINICAL STUDIES (14.6)*].

### **8.6 Renal Impairment**

The effect of renal impairment on the pharmacokinetics of norethindrone acetate and ethinyl estradiol has not been studied.

### **8.7 Hepatic Impairment**

The effect of hepatic impairment on the pharmacokinetics of norethindrone acetate and ethinyl estradiol has not been studied.

## 10 OVERDOSAGE

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

## 11 DESCRIPTION

Fyavolv (norethindrone acetate and ethinyl estradiol tablets USP) is a continuous dosage regimen of a progestin-estrogen combination for oral administration.

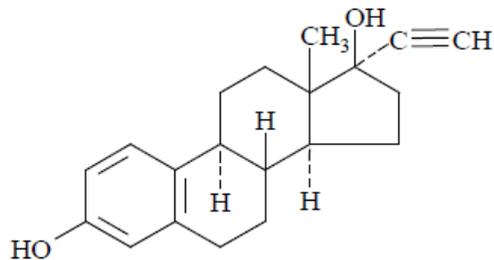
The following two strengths of Fyavolv tablets are available:

Fyavolv (0.5 mg/0.0025 mg): Each white to off-white, round film-coated tablet, debossed with “F51” on one side and “LU” on the other side contains 0.5 mg norethindrone acetate and 0.0025 mg ethinyl estradiol.

Fyavolv (1 mg/0.005 mg): Each blue, round film-coated tablet, debossed with “F52” on one side and “LU” on the other side contains 1 mg norethindrone acetate and 0.005 mg ethinyl estradiol.

Each tablet contains the following inactive ingredients: calcium stearate, corn starch, hypromellose, lactose monohydrate, microcrystalline cellulose, polyethylene glycol 400, titanium dioxide and vitamin E. Each tablet of 1 mg/0.005 mg also contains FD&C Blue No. 2 Aluminum Lake.

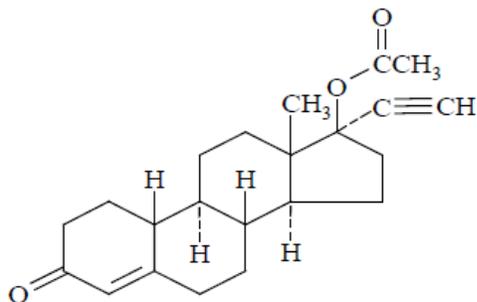
The structural formulas are as follows.



Ethinyl Estradiol [19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol, (17 $\alpha$ )-]

Molecular Weight: 296.40

Molecular Formula: C<sub>20</sub>H<sub>24</sub>O<sub>2</sub>



Norethindrone Acetate [19-Norpregn-4-en-20-yn-3-one, 17-(acetyloxy)-, (17 $\alpha$ )-]

Molecular Weight: 340.46

Molecular Formula: C<sub>22</sub>H<sub>28</sub>O<sub>3</sub>

## **12 CLINICAL PHARMACOLOGY**

### **12.1 Mechanism of Action**

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

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

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

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

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. Progestins 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. Progestins produce similar endometrial changes to those of the naturally occurring hormone progesterone.

### **12.2 Pharmacodynamics**

Currently, there are no pharmacodynamic data known for norethindrone acetate and ethinyl estradiol.

### **12.3 Pharmacokinetics**

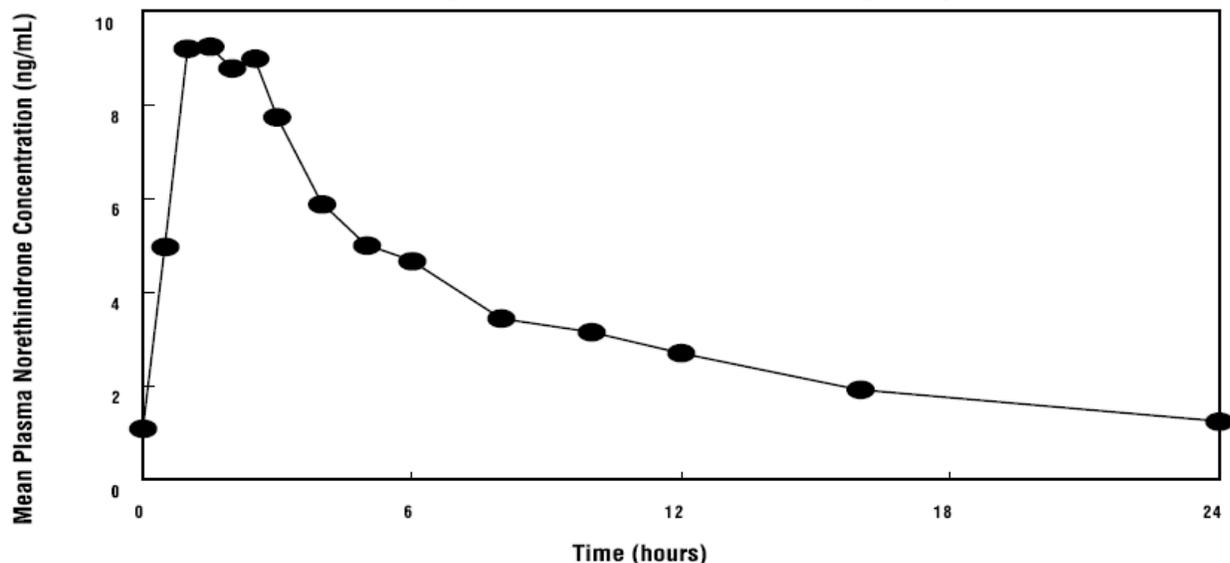
#### ***Absorption***

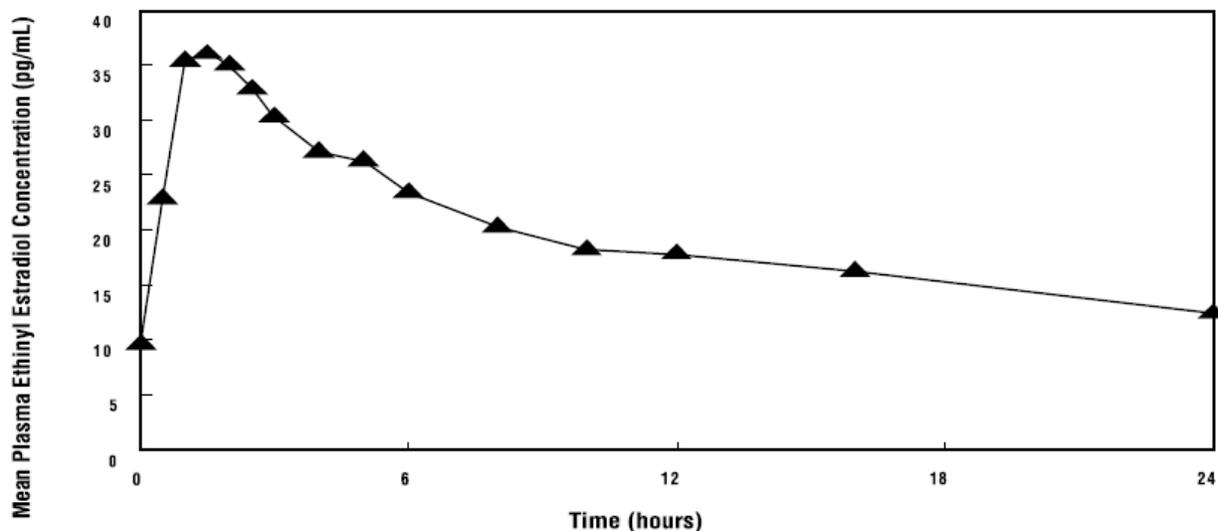
Norethindrone acetate (NA) is completely deacetylated to norethindrone after oral administration, and the disposition of norethindrone acetate is indistinguishable from that of orally administered norethindrone. Norethindrone acetate and ethinyl estradiol (EE) are absorbed from norethindrone acetate and ethinyl estradiol 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 an absolute bioavailability of approximately 64 percent for norethindrone and 55 percent for ethinyl estradiol. Bioavailability of norethindrone acetate and ethinyl estradiol tablet is similar to that from solution for

norethindrone and slightly less for ethinyl estradiol. Administration of norethindrone acetate and ethinyl estradiol tablets with a high fat meal decreases rate but not extent of ethinyl estradiol absorption. The extent of norethindrone absorption is increased by 27 percent following administration of norethindrone acetate and ethinyl estradiol tablets with food.

The full pharmacokinetic profile of norethindrone acetate and ethinyl estradiol tablet was not characterized due to assay sensitivity limitations. However, the multiple-dose pharmacokinetics were studied at a dose of 1 mg norethindrone acetate and 0.01 mg ethinyl estradiol in 18 postmenopausal women. Mean plasma concentrations are shown below (Figure 1) and pharmacokinetic parameters are found in Table 2. Based on a population pharmacokinetic analysis, mean steady-state concentrations of norethindrone for 1 mg norethindrone acetate and 0.005 mg ethinyl estradiol and 1/10 are slightly more than proportional to dose when compared to 0.5 mg norethindrone acetate and 0.0025 mg ethinyl estradiol tablets. It can be explained by higher SHBG concentrations. Mean steady-state plasma concentrations of ethinyl estradiol for the norethindrone acetate and ethinyl estradiol 0.5/2.5 tablets and norethindrone acetate and ethinyl estradiol 1/5 tablets are proportional to dose, but there is a less than proportional increase in steady-state concentrations for the norethindrone acetate and ethinyl estradiol 1/10 tablet.

**Figure 1. Mean Steady-State (Day 87) Plasma Norethindrone and Ethinyl Estradiol Concentrations Following Continuous Oral Administration of 1 mg Norethindrone Acetate and 0.01 mg Ethinyl Estradiol Tablets**





**Table 2. Mean (SD) Single-Dose (Day 1) and Steady-State (Day 87) Pharmacokinetic Parameters<sup>a</sup> Following Administration of 1 mg Norethindrone Acetate and 0.01 mg Ethinyl Estradiol Tablets**

	$C_{max}$	$t_{max}$	$AUC_{(0-24)}$	CL/F	$t_{1/2}$
<b>Norethindrone</b>	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)
<b>Ethinyl Estradiol</b>	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>  $C_{max}$  = 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

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

Based on a population pharmacokinetic analysis, average steady-state concentrations ( $C_{ss}$ ) of norethindrone and ethinyl estradiol for norethindrone acetate and ethinyl estradiol 1/5 tablets are estimated to be 2.6 ng/mL and 11.4 pg/mL, respectively.  $C_{ss}$  values of norethindrone and ethinyl estradiol for norethindrone acetate and ethinyl estradiol 0.5/2.5 tablets are estimated to be 1.1 ng/mL and 5.4 pg/mL, respectively.

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

### ***Distribution***

The distribution of exogenous estrogens is similar to that of endogenous estrogens. Estrogens are widely distributed in the body and are generally found in higher concentrations in the sex hormone target organs. Estrogens circulate in the blood largely bound to SHBG and albumin.

Volume of distribution of norethindrone and ethinyl estradiol ranges from 2 to 4 L/kg. Plasma protein binding of both steroids is extensive (greater than 95 percent); norethindrone binds to both albumin and SHBG, whereas ethinyl estradiol binds only to albumin. Although ethinyl estradiol does not bind to SHBG, it induces SHBG synthesis.

### ***Metabolism***

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

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, both by oxidation and by conjugation with sulfate and glucuronide. Sulfates are the major circulating conjugates of ethinyl estradiol and glucuronides predominate in 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***

Estradiol, estrone, and estriol are excreted in the urine along with glucuronide and sulfate conjugates.

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 1 mg norethindrone acetate and 0.01 mg ethinyl estradiol tablets are approximately 13 hours and 24 hours, respectively.

### ***Use in Specific Populations***

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

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

## 14 CLINICAL STUDIES

### 14.1 Effects on Vasomotor Symptoms

A 12-week placebo-controlled, multicenter, randomized clinical trial was conducted in 266 symptomatic women 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.

A total of 66 women were randomized to receive norethindrone acetate and ethinyl estradiol 1/5 and 66 women were randomized to the placebo group. Norethindrone acetate and ethinyl estradiol 1/5 was shown to be statistically better than placebo at weeks 4 and 12 for relief of the frequency of moderate to severe vasomotor symptoms (see Table 3). In Table 4, norethindrone acetate and ethinyl estradiol 1/5 was shown to be statistically better than placebo at weeks 4 and 12 for relief of the severity of moderate to severe vasomotor symptoms.

**Table 3. Mean Change from Baseline in the Number of Moderate to Severe Vasomotor Symptoms per Week - ITT Population, LOCF**

Visit	Placebo (N = 66)	Norethindrone Acetate and Ethinyl Estradiol 0.5/2.5 (N = 67)	Norethindrone Acetate and Ethinyl Estradiol 1/5 (N = 66)
<b>Baseline [1]</b>			
Mean (SD)	76.5 (21.4)	77.6 (26.5)	70.0 (16.6)
<b>Week 4</b>			
Mean (SD)	39.4 (27.6)	30.2 (26.1)	20.4 (22.7)
Mean Change from Baseline (SD)	-37.0 (26.6)	-47.4* (26.1)	-49.6* (22.1)
p-Value vs. Placebo (95 percent CI) [2]		0.041 (-20.0, -1.0)	<0.001 (-22.0,-6.0)
<b>Week 12</b>			
Mean (SD)	31.1 (27.0)	13.8 (20.4)	11.3 (18.9)
Mean Change from Baseline (SD)	-45.3 (30.2)	-63.8* (27.5)	-58.7* (23.1)
p-Value vs. Placebo (95 percent CI) [2]		<0.001 (-27.0, -7.0)	<0.001 (-25.0, -5.0)

\* Denotes statistical significance at the 0.05 level

[1] The baseline number of moderate to severe vasomotor symptoms (MSVS) is the weekly average number of MSVS during the two week pre-randomization observation period.

[2] ANCOVA -Analysis of Covariance model where the observation variable is change from baseline; independent variables include treatment, center and baseline as covariate. The 95 percent CI -Mann-Whitney confidence interval for the difference between means (not stratified by center).

ITT = intent to treat; LOCF = last observation carried forward; CI = confidence interval 2 randomized subjects (1 in Placebo and 1 in norethindrone acetate and ethinyl estradiol) did not return diaries.

**Table 4. Mean Change from Baseline in the Daily Severity Score of Moderate to Severe Vasomotor Symptoms per Week -ITT Population, LOCF**

Visit	Placebo (N = 66)	Norethindrone Acetate and Ethinyl Estradiol 0.5/2.5 (N = 67)	Norethindrone Acetate and Ethinyl Estradiol 1/5 (N = 66)
<b>Baseline [1]</b>			
Mean (SD)	2.49 (0.26)	2.48 (0.22)	2.47 (0.23)
<b>Week 4</b>			
Mean (SD)	2.13 (0.74)	1.88 (0.89)	1.45 (1.03)
Mean Change from Baseline (SD)	-0.36 (0.68)	-0.59 (0.83)	-1.02* (1.06)
p-Value vs. Placebo (95 percent CI) [2]	-	0.130 (-0.3, 0.0)	<0.001 (-0.9, -0.2)
<b>Week 5</b>			
Mean (SD)	2.06 (0.79)	1.68 (0.99)	1.23 (1.03)
Mean Change from Baseline (SD)	-0.44 (0.74)	-0.80* (0.94)	-1.24* (1.07)
p-Value vs. Placebo (95 percent CI) [2]		0.041 (-0.4, -0.0)	<0.001 (-1.2, -0.3)
<b>Week 12</b>			
Mean (SD)	1.82 (1.03)	1.22 (1.11)	1.02 (1.16)
Mean Change from Baseline (SD)	-0.67 (1.02)	-1.26* (1.08)	-1.45* (1.19)
p-Value vs. Placebo (95 percent CI) [2]	-	0.002 (-0.9, -0.2)	<0.001 (-1.4, -0.3)

\* Denotes statistical significance at the 0.05 level

[1] The baseline severity of moderate to severe vasomotor symptoms (MSVS) is the daily severity score of MSVS during the two week pre-randomization observation period.

[2] ANCOVA -Analysis of Covariance model where the observation variable is change from baseline; independent variables include treatment, center and baseline as covariate. The 95 percent CI -Mann-Whitney confidence interval for the difference between means (not stratified by center).

ITT = intent to treat; LOCF = last observation carried forward; CI = confidence interval 2 randomized subjects (1 in Placebo and 1 in norethindrone acetate and ethinyl estradiol) did not return diaries.

## 14.2 Effects on the Endometrium

A 2-year, placebo-controlled, multicenter, randomized clinical trial was conducted to determine the safety and efficacy of norethindrone acetate and ethinyl estradiol on maintaining bone mineral density, protecting the endometrium, and to determine effects on lipids. A total of 1,265 women were enrolled and randomized to either placebo, 0.2 mg norethindrone acetate/1 mcg ethinyl estradiol (NA/EE 0.2/1), 0.5 mg norethindrone acetate/2.5 mcg ethinyl estradiol (NA/EE 0.5/2.5), norethindrone acetate and ethinyl estradiol 1/5 and 1 mg norethindrone acetate/10 mcg ethinyl estradiol (NA/EE 1/10) or matching unopposed EE doses (1, 2.5, 5, or 10 mcg) for a total of 9 treatment groups. All participants received 1000 mg of calcium supplementation daily. Of the 1,265 women randomized to the various treatment arms of this study, 137 were randomized to placebo, 146 to norethindrone acetate and ethinyl estradiol 1/5, 136 to norethindrone acetate/ethinyl estradiol 0.5/2.5 and 141 to EE 5 mcg and 137 to EE 2.5 mcg. Of these, 134 placebo, 143 norethindrone acetate and ethinyl estradiol 1/5, 136 norethindrone acetate/ethinyl estradiol 0.5/2.5, 139 EE 5 mcg and 137 EE 2.5 mcg had a baseline endometrial result. Baseline

biopsies were classified as normal (in approximately 95 percent of subjects), or insufficient tissue (in approximately 5 percent of subjects). Follow-up biopsies were obtained in approximately 70 to 80 percent of patients in each arm after 12 and 24 months of therapy. Results for norethindrone acetate and ethinyl estradiol 1/5 and appropriate comparators are shown in [Table 5](#).

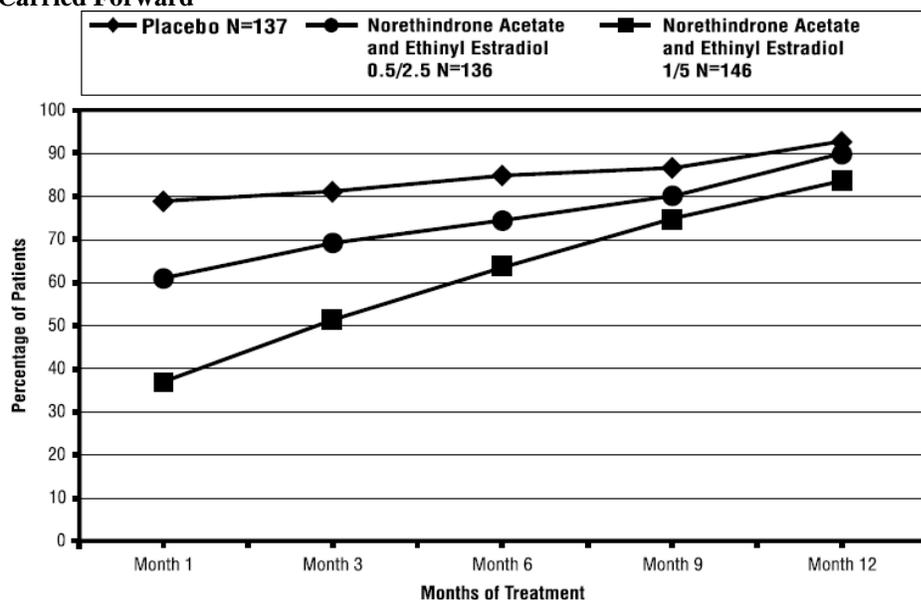
**Table 5. Endometrial Biopsy Results After 12 and 24 Months of Treatment (CHART Study, 376 to 359)**

Endometrial Status	Placebo	Norethindrone Acetate and Ethinyl Estradiol		EE Alone	
		0.5/2.5	1/5	2.5 mcg	5 mcg
<b>Number of Patients Biopsied at Baseline</b>	N = 134	N = 136	N = 143	N = 137	N = 139
<b>MONTH 12 (Percent Patients)</b>					
Patients Biopsied (percent)	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 (Percent Patients)</b>					
Patients Biopsied (percent)	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

### 14.3 Effects on Uterine Bleeding or Spotting

The cumulative incidence of amenorrhea, defined as no bleeding or spotting obtained from subject recall, was evaluated over 12 months for norethindrone acetate and ethinyl estradiol 1/5 and placebo arms. Results are shown in [Figure 2](#).

**Figure 2. Patients With Cumulative Amenorrhea Over Time: Intent-to-Treat Population, Last Observation Carried Forward**

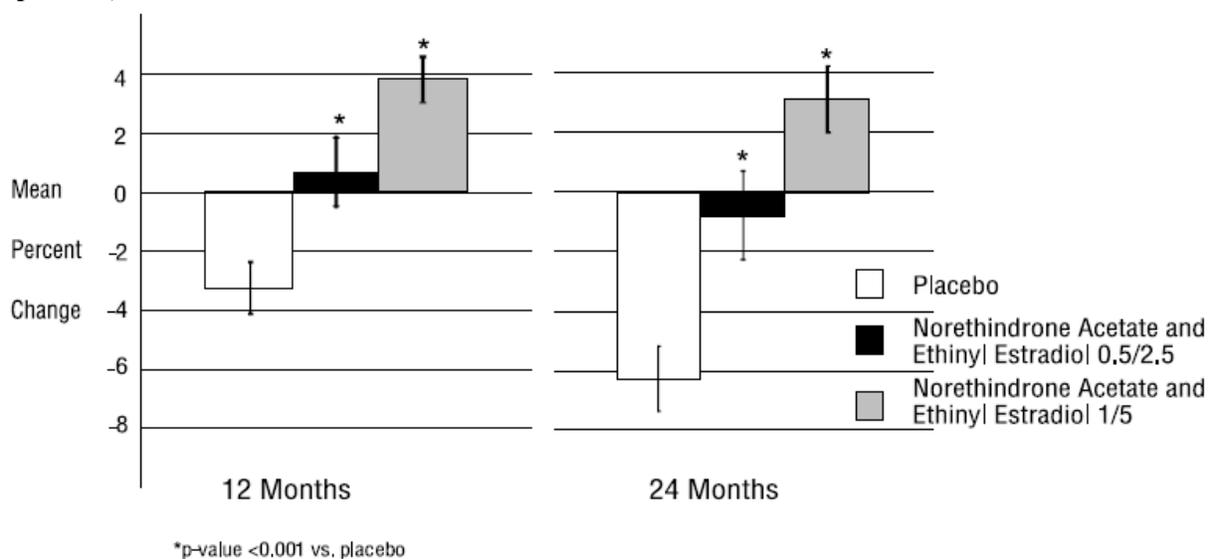


#### 14.4 Effect on Bone Mineral Density

In the 2 year study, trabecular BMD was assessed at lumbar spine using quantitative computed tomography. A total of 419 postmenopausal primarily Caucasian women, 40 to 64 years of age, with intact uteri and nono-steoporotic bone mineral densities were randomized (1:1:1) to norethindrone acetate and ethinyl estradiol 1/5, norethindrone acetate and ethinyl estradiol 0.5/2.5 or placebo. Approximately 75 percent of the subjects in each group completed the two-year study. All patients received 1000 mg calcium in divided doses. Vitamin D was not supplemented.

As shown in [Figure 3](#), women treated with norethindrone acetate and ethinyl estradiol 1/5 had an average increase of 3.1 percent in lumbar spine BMD from baseline to Month 24. Women treated with placebo had average decreases of -6.3 percent in spinal BMD from baseline to Month 24. The differences in the changes from baseline to Month 24 in the norethindrone acetate and ethinyl estradiol 1/5 group compared with the placebo group was statistically significant.

**Figure 3. Mean Percent Change (+ SE) From Baseline in Volumetric Bone Mineral Density\* at Lumbar Spine Measured by Quantitative Computed Tomography after 12 and 24 Months of Treatment (Intent-to-Treat Population)**



\* It should be noted that when measured by QCT, BMD gains and losses are greater than when measured by dual X-ray absorptiometry (DXA). Therefore, the differences in the changes in BMD between the placebo and active drug treated groups will be larger when measured by QCT compared with DXA. Changes in BMD measured by DXA should not be compared with changes in BMD measured by QCT.

#### 14.5 Women's Health Initiative Studies

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

### **WHI Estrogen Plus Progestin Substudy**

The WHI estrogen plus progestin substudy was stopped early. According to the predefined stopping rule, after an average follow-up of 5.6 years of treatment, the increased risk of invasive breast cancer and cardiovascular events exceeded the specified benefits included in the “global index”. The absolute excess risk of events included in the “global index” was 19 per 10,000 women-years.

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

Results of the CE plus MPA substudy, which included 16,608 women (average 63 years of age, range 50 to 79; 83.9 percent White, 6.8 percent Black, 5.4 percent Hispanic, 3.9 percent Other) are presented in [Table 6](#). These results reflect centrally adjudicated data after an average follow-up of 5.6 years.

**Table 6. Relative and Absolute Risk Seen in the Estrogen Plus Progestin Substudy of WHI at an Average of 5.6 Years<sup>a,b</sup>**

Event	Relative Risk CE/MPA vs. Placebo (95 percent nCI <sup>c</sup> )	CE/MPA n = 8,506	Placebo n = 8,102
		Absolute Risk per 10,000 Women-Years	
CHD events	1.23 (0.99 to 1.53)	41	34
<i>Non-fatal MI</i>	<i>1.28 (1.00 to 1.63)</i>	<i>31</i>	<i>25</i>
<i>CHD death</i>	<i>1.10 (0.70 to 1.75)</i>	<i>8</i>	<i>8</i>
All strokes	1.31 (1.03 to 1.68)	33	25
<i>Ischemic stroke</i>	<i>1.44 (1.09 to 1.90)</i>	<i>26</i>	<i>18</i>
Deep vein thrombosis <sup>d</sup>	1.95 (1.43 to 2.67)	26	13
Pulmonary embolism	2.13 (1.45 to 3.11)	18	8
Invasive breast cancer <sup>e</sup>	1.24 (1.01 to 1.54)	41	33
Colorectal cancer	0.61 (0.42 to 0.87)	10	16
Endometrial cancer <sup>d</sup>	0.81 (0.48 to 1.36)	6	7
Cervical cancer <sup>d</sup>	1.44 (0.47 to 4.42)	2	1
Hip fracture	0.67 (0.47 to 0.96)	11	16
Vertebral fractures <sup>d</sup>	0.65 (0.46 to 0.92)	11	17
Lower arm/wrist fractures <sup>d</sup>	0.71 (0.59 to 0.85)	44	62
Total fractures <sup>d</sup>	0.76 (0.69 to 0.83)	152	199
Overall Mortality <sup>e,f</sup>	1.00 (0.83 to 1.19)	52	52
Global Index <sup>g</sup>	1.13 (1.02 to 1.25)	184	165

<sup>a</sup> Adapted from numerous WHI publications. WHI publications can be viewed at [www.nhlbi.nih.gov/whi](http://www.nhlbi.nih.gov/whi).

<sup>b</sup> Results are based on centrally adjudicated data.

<sup>c</sup> Nominal confidence intervals unadjusted for multiple looks and multiple comparisons.

<sup>d</sup> Not included in “global index”.

<sup>e</sup> Includes metastatic and non-metastatic breast cancer with the exception of in situ cancer.

<sup>f</sup> All deaths, except from breast or colorectal cancer, definite or probable CHD, PE or cerebrovascular disease.

<sup>g</sup> A subset of the events was combined in a “global index” defined as the earliest occurrence of CHD events, invasive breast cancer, stroke, pulmonary embolism, colorectal cancer, hip fracture, or death due to other causes.

Timing of the initiation of estrogen plus progestin therapy relative to the start of menopause may affect the overall risk benefit profile. The WHI estrogen plus progestin substudy stratified by age showed in women 50 to 59 years of age, a non-significant trend toward reduced risk for overall mortality [hazard ratio (HR) 0.69 (95 percent CI, 0.44 to 1.07)].

### WHI Estrogen-Alone Substudy

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

Results of the estrogen-alone substudy, which included 10,739 women (average 63 years of age, range 50 to 79; 75.3 percent White, 15.1 percent Black, 6.1 percent Hispanic, 3.6 percent Other), after an average follow-up of 7.1 years, are presented in [Table 7](#).

**Table 7. Relative and Absolute Risk Seen in the Estrogen-Alone Substudy of WHI<sup>a</sup>**

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

<sup>a</sup> Adapted from numerous WHI publications. WHI publications can be viewed at [www.nhlbi.nih.gov/whi](http://www.nhlbi.nih.gov/whi).

<sup>b</sup> Nominal confidence intervals unadjusted for multiple looks and multiple comparisons.

<sup>c</sup> Results are based on centrally adjudicated data for an average follow-up of 7.1 years.

<sup>d</sup> Not included in “global index”.

<sup>e</sup> Results are based on an average follow-up of 6.8 years.

<sup>f</sup> All deaths, except from breast or colorectal cancer, definite or probable CHD, PE or cerebrovascular disease.<sup>g</sup> A subset of the events was combined in a “global index” defined as the earliest occurrence of CHD events, invasive breast cancer, stroke, pulmonary embolism, colorectal cancer, hip fracture, or death due to other causes.

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

No overall difference for primary CHD events (nonfatal MI, silent MI and CHD death) and invasive breast cancer incidence in women receiving CE-alone compared with placebo was reported in final centrally adjudicated results from the estrogen-alone substudy, after an average follow-up of 7.1 years (see [Table 7](#)).

Centrally adjudicated results for stroke events from the estrogen-alone substudy, after an average follow-up of 7.1 years, reported no significant difference in distribution of stroke subtype or severity, including fatal strokes, in women receiving CE-alone compared to placebo. Estrogen-alone therapy increased the risk of ischemic stroke, and this excess was present in all subgroups of women examined<sup>10</sup> (see [Table 7](#)).

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

#### **14.6 Women's Health Initiative Memory Study**

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

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

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

After an average follow-up of 5.2 years, the relative risk of probable dementia for CE-alone versus placebo was 1.49 (95 percent CI, 0.83 to 2.66). The absolute risk of probable dementia for CE-alone versus placebo was 37 versus 25 cases per 10,000 women-years. Probable dementia as defined in this study included AD, VaD and mixed types (having features of both AD and VaD). The most common classification of probable dementia in the treatment group and the placebo group was AD. Since the ancillary study was conducted in women 65 to 79 years of age, it is

unknown whether these findings apply to younger postmenopausal women [see WARNINGS AND PRECAUTIONS (5.3), and USE IN SPECIFIC POPULATIONS (8.5)].

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

## 15 REFERENCES

1. Rossouw JE, et al. Postmenopausal Hormone Therapy and Risk of Cardiovascular Disease by Age and Years Since Menopause. *JAMA*. 2007;297:1465-1477.
2. Hsia J, et al. Conjugated Equine Estrogens and Coronary Heart Disease. *Arch Int Med*. 2006;166:357-365.
3. Cushman M, et al. Estrogen Plus Progestin and Risk of Venous Thrombosis. *JAMA*. 2004;292:1573-1580.
4. Curb JD, et al. Venous Thrombosis and Conjugated Equine Estrogen in Women Without a Uterus. *Arch Int Med*. 2006;166:772-780.
5. Chlebowski RT, et al. Influence of Estrogen Plus Progestin on Breast Cancer and Mammography in Healthy Postmenopausal Women. *JAMA*. 2003;289:3234-3253.
6. Stefanick ML, et al. Effects of Conjugated Equine Estrogens on Breast Cancer and Mammography Screening in Postmenopausal Women With Hysterectomy. *JAMA*. 2006;295:1647-1657.
7. Anderson GL, et al. Effects of Estrogen Plus Progestin on Gynecologic Cancers and Associated Diagnostic Procedures. *JAMA*. 2003;290:1739-1748.
8. Shumaker SA, et al. Conjugated Equine Estrogens and Incidence of Probable Dementia and Mild Cognitive Impairment in Postmenopausal Women. *JAMA*. 2004;291:2947-2958.
9. Jackson RD, et al. Effects of Conjugated Equine Estrogen on Risk of Fractures and BMD in Postmenopausal Women With Hysterectomy: Results From the Women's Health Initiative Randomized Trial. *J Bone Miner Res*. 2006;21:817-828.
10. Hendrix SL, et al. Effects of Conjugated Equine Estrogen on Stroke in the Women's Health Initiative. *Circulation*. 2006;113:2425-2434.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

### 16.1 How Supplied

Fyavolv 0.5 mg/0.0025 mg are white to off-white, round film-coated tablets debossed with "F51" on one side and "LU" on the other side containing 0.5 mg of norethindrone acetate and 0.0025 mg of ethinyl estradiol.

Fyavolv 0.5 mg/0.0025 mg are available in bottle of 90 tablets (NDC 68180-827-09) and in a wallet (NDC 68180-827-11) containing 28 tablets enclosed in a pouch, such 3 pouches are packed in a carton (NDC 68180-827-13).

Fyavolv 1 mg/0.005 mg are blue, round film-coated tablets debossed with "F52" on one side and "LU" on the other side containing 1 mg of norethindrone acetate and 0.005 mg of ethinyl estradiol.

Fyavolv 1 mg/0.005 mg are available in bottle of 90 tablets (NDC 68180-828-09) and in a wallet (NDC 68180-828-11) containing 28 tablets enclosed in a pouch, such 3 pouches are packed in a carton (NDC 68180-828-13).

### **16.2 Storage and Handling**

Keep this drug and all drugs out of the reach of children.

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

## **17 PATIENT COUNSELING INFORMATION**

See FDA-approved patient labeling (Patient Information)

### **17.1 Abnormal Vaginal Bleeding**

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

### **17.2 Possible Serious Adverse Reactions with Estrogen Plus Progestin Therapy**

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

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

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

Distributed by:

**Lupin Pharmaceuticals, Inc.**

Baltimore, Maryland 21202

United States

Manufactured by:

**Lupin Limited**

Pithampur (M.P.) - 454 775

India

September 2015

ID#: 238473

**PATIENT INFORMATION**  
**Fyavolv™ (FYE-uh-volv)**  
**(norethindrone acetate and ethinyl estradiol tablets USP)**  
**0.5 mg/0.0025 mg and 1 mg/0.005 mg**

Read this Patient Information before you start taking Fyavolv and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your menopausal symptoms or your treatment.

**What is the most important information I should know about Fyavolv (a combination of estrogen and progestin)?**

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

**What is Fyavolv?**

Fyavolv is a prescription medicine that contains two kinds of hormones, an estrogen and a progestin.

**What is Fyavolv used for?**

Fyavolv is used after menopause to:

• **Reduce moderate to severe hot flashes**

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

When estrogen levels begin dropping, some women get very uncomfortable symptoms, such as feelings of warmth in the face, neck, and chest, or sudden intense episodes of heat and sweating ("hot flashes" or "hot flushes"). In some women the symptoms are mild, and they will not need to take estrogens. In other women, symptoms can be more severe.

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

If you use Fyavolv only to prevent osteoporosis from menopause, talk with your healthcare provider about whether a different treatment or medicine without estrogens might be better for you. You and your healthcare provider should talk regularly about whether you still need treatment with Fyavolv.

### **Who should not take Fyavolv?**

#### **Do not take Fyavolv if you have had your uterus (womb) removed (hysterectomy).**

Fyavolv contains a progestin to decrease the chance of getting cancer of the uterus. If you do not have a uterus, you do not need a progestin and you should not take Fyavolv.

#### **Do not take Fyavolv if you:**

- **have unusual vaginal bleeding**  
Vaginal bleeding after menopause may be a warning sign of cancer of the uterus (womb). Your healthcare provider should check any unusual vaginal bleeding to find out the cause.
- **currently have or have had certain cancers.**  
Estrogens may increase the chance of getting certain types of cancers, including cancer of the breast or uterus. If you have or have had cancer, talk with your healthcare provider about whether you should take Fyavolv.
- **had a stroke or heart attack**
- **currently have or have had blood clots**
- **currently have or have had liver problems**
- **have been diagnosed with a bleeding disorder**
- **are allergic to Fyavolv or any of its ingredients.**  
See the list of ingredients in Fyavolv at the end of this leaflet.
- **think you may be pregnant**  
Fyavolv is not for pregnant women. If you think you may be pregnant, you should have a pregnancy test and know the results. Do not take Fyavolv if the test is positive and talk to your healthcare provider.

### **What should I tell my healthcare provider before I take Fyavolv?**

#### **Before you take Fyavolv, tell your healthcare provider if you:**

- **have any unusual vaginal bleeding**  
Vaginal bleeding after menopause may be a warning sign of cancer of the uterus (womb). Your healthcare provider should check any unusual vaginal bleeding to find out the cause.
- **have any other medical conditions**  
Your healthcare provider may need to check you more carefully if you have certain conditions, such as asthma (wheezing), epilepsy (seizures), diabetes, migraine, endometriosis, lupus, angioedema (swelling of face and tongue), or problems with your heart, liver, thyroid, kidneys, or have high calcium levels in your blood.
- **are going to have surgery or will be on bed rest**  
Your healthcare provider will let you know if you need to stop taking Fyavolv.
- **are breastfeeding**  
The hormones in Fyavolv can pass into your breast milk.

#### **Tell your healthcare provider about all the medicines you take,**

including prescription and non-prescription medicines, vitamins, and herbal supplements. Some medicines may affect how Fyavolv works. Fyavolv may also affect how your other medicines

work. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new medicine.

### **How should I take Fyavolv?**

- Take Fyavolv exactly as your healthcare provider tells you to take it.
- Take 1 Fyavolv tablet at the same time each day.
- You and your healthcare provider should talk regularly (every 3 to 6 months) about the dose you are taking and whether or not you still need treatment with Fyavolv.

### **What are the possible side effects of Fyavolv?**

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

#### **Serious, but less common side effects include:**

- heart attack
- stroke
- blood clots
- dementia
- breast cancer
- cancer of the lining of the uterus (womb)
- cancer of the ovary
- high blood pressure
- high blood sugar
- gallbladder disease
- liver problems
- changes in your thyroid hormone levels
- enlargement of benign tumors of the uterus (“fibroids”)

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

- new breast lumps
- unusual vaginal bleeding
- changes in vision or speech
- sudden new severe headaches
- severe pains in your chest or legs with or without shortness of breath, weakness and fatigue

#### **Less serious, but common side effects include:**

- headache
- breast pain
- irregular vaginal bleeding or spotting
- stomach or abdominal cramps, bloating
- hair loss
- fluid retention
- vaginal yeast infection

These are not all the possible side effects of Fyavolv. For more information, ask your healthcare provider or pharmacist. Tell your healthcare provider if you have any side effects that bother you or does not go away.

You may report side effects to Lupin Pharmaceuticals, Inc. at 1-800-399-2561 or FDA at 1-800-FDA-1088.

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

- Talk with your healthcare provider regularly about whether you should continue taking Fyavolv.
- If you have a uterus, talk with your healthcare provider about whether the addition of a progestin is right for you.
- The addition of a progestin is generally recommended for a woman with a uterus to reduce the chance of getting cancer of the uterus (womb).
- See your healthcare provider right away if you develop vaginal bleeding while taking Fyavolv.
- Have a pelvic exam, breast exam and mammogram (breast x-ray) every year unless your healthcare provider tells you something else.
- If members of your family have had breast cancer or if you have ever had breast lumps or an abnormal mammogram (breast x-ray), you may need to have breast exams more often.
- If you have high blood pressure, high cholesterol (fat in the blood), diabetes, are overweight, or use tobacco, you may have a higher chance for getting heart disease.

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

**How should I store Fyavolv?**

- Store at 25°C (77°F); excursions permitted to 15 to 30°C (59 to 86°F) [see USP controlled room temperature].

**Keep Fyavolv out of the reach of children.**

**General information about the safe and effective use of Fyavolv.**

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

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

For more information go to [www.lupinpharmaceuticals.com](http://www.lupinpharmaceuticals.com) or call 1-800-399-2561.

**What are the ingredients in Fyavolv?**

**Active Ingredients:** norethindrone acetate and ethinyl estradiol

**Inactive Ingredients:** calcium stearate, corn starch, hypromellose, lactose monohydrate, microcrystalline cellulose, polyethylene glycol 400, titanium dioxide, vitamin E. Each tablet of 1 mg/0.005 mg also contains FD&C Blue No. 2 Aluminum Lake.

This Patient Information has been approved by the U.S Food and Drug Administration.

Fyavolv™ is a trademark of Lupin Pharmaceuticals, Inc.

The other brands listed are trademarks of their respective owners and are not trademarks of Lupin Pharmaceuticals, Inc. The makers of these brands are not affiliated with and do not endorse Lupin Pharmaceuticals, Inc. or its products.

Distributed by:

**Lupin Pharmaceuticals, Inc.**

Baltimore, Maryland 21202

United States

Manufactured by:

**Lupin Limited**

Pithampur (M.P.) - 454 775

India

September 2015

ID#: 238475