

# **NORETHINDRONE ACETATE AND ETHINYL ESTRADIOL- norethindrone acetate and ethinyl estradiol tablet**

## **Glenmark Pharmaceuticals Inc., USA**

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### **HIGHLIGHTS OF PRESCRIBING INFORMATION**

These highlights do not include all the information needed to use NORETHINDRONE ACETATE AND ETHINYL ESTRADIOL safely and effectively. See full prescribing information for NORETHINDRONE ACETATE AND ETHINYL ESTRADIOL.

**NORETHINDRONE ACETATE and ETHINYL ESTRADIOL tablets, for oral use**  
Initial U.S. Approval: 1968

**WARNING: CARDIOVASCULAR DISORDERS, PROBABLE DEMENTIA, BREAST CANCER, and ENDOMETRIAL CANCER**

*See full prescribing information for complete boxed warning.*

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

- **The Women’s Health Initiative (WHI) estrogen plus progestin substudy reported increased risks of pulmonary embolism (PE), deep vein thrombosis (DVT), stroke, and myocardial infarction (MI) (5.1)**
- **The WHI estrogen plus progestin substudy reported 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)**
- **Do not use estrogen plus progestin therapy for the prevention of cardiovascular disease or dementia (5.1, 5.3)**

#### **Estrogen-Along Therapy**

- **There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens (5.2)**
- **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)**
- **Do not use estrogen-alone therapy for the prevention of cardiovascular disease or dementia (5.1, 5.3)**

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

Boxed Warning 5/2023

Warnings and Precautions, Malignant Neoplasms (5.2) 11/2023

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

Norethindrone acetate and ethinyl estradiol tablets are a combination of an estrogen and 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 orally once daily (2.1, 2.2)

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

- Round, light pink to light tablet contains 0.5 mg norethindrone acetate and 2.5 mcg ethinyl estradiol (3)
- Round, white to off-white tablet contains 1 mg norethindrone acetate and 5 mcg ethinyl estradiol (3)

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## CONTRAINDICATIONS

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- Undiagnosed abnormal genital bleeding (4, 5.2)
- Breast cancer or a history of breast cancer (4, 5.2)
- 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, angioedema or hypersensitivity to norethindrone acetate and ethinyl estradiol tablets (4)
- Hepatic impairment or disease (4, 5.10)
- Protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders (4)

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## WARNINGS AND PRECAUTIONS

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- 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)

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## ADVERSE REACTIONS

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Most common adverse reactions with norethindrone acetate and ethinyl estradiol tablets (incidence greater than or equal to 5 percent) are: headache, abdominal pain, breast pain, and edema (generalized). (6.1) (6)

**To report SUSPECTED ADVERSE REACTIONS, contact Glenmark Pharmaceuticals Inc., USA at 1 (888) 721-7115 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch). (6)**

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## DRUG INTERACTIONS

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Inducers and/or inhibitors of CYP3A4 may affect estrogen drug metabolism and decrease or increase the estrogen plasma concentration. (7.1) (7)

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

**Revised: 11/2023**

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## FULL PRESCRIBING INFORMATION: CONTENTS\*

### WARNING: CARDIOVASCULAR DISORDERS, PROBABLE DEMENTIA, BREAST CANCER, and ENDOMETRIAL CANCER

#### 1 INDICATIONS AND USAGE

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 Progestogen When a Woman Has Not Had a Hysterectomy

5.8 Elevated Blood Pressure

5.9 Exacerbation of Hypertriglyceridemia

- 5.10 Hepatic Impairment and/or a Past History of Cholestatic Jaundice
- 5.11 Exacerbation of 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**

## **8 USE IN SPECIFIC POPULATIONS**

- 8.1 Pregnancy
- 8.2 Lactation
- 8.4 Pediatric Use
- 8.5 Geriatric Use

## **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 in Postmenopausal Women
- 14.2 Effects on the Endometrium
- 14.3 Effects on Uterine Bleeding or Spotting in Postmenopausal Women
- 14.4 Effect on Bone Mineral Density in Postmenopausal Women
- 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**

### **Vaginal Bleeding**

### **Possible Serious Adverse Reactions with Estrogen Plus Progestogen Therapy**

### **Possible Common Adverse Reactions with Estrogen Plus Progestogen Therapy**

\* Sections or subsections omitted from the full prescribing information are not listed.

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## **FULL PRESCRIBING INFORMATION**

**WARNING: CARDIOVASCULAR DISORDERS, PROBABLE DEMENTIA,  
BREAST CANCER, and ENDOMETRIAL CANCER**

**Estrogen Plus Progestin Therapy**

**Cardiovascular Disorders and Probable Dementia**

The Women's Health Initiative (WHI) estrogen plus progestin substudy reported increased risks of pulmonary embolism (PE), deep vein thrombosis (DVT), 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 WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age and 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)*].

Do not use estrogen plus progestogen therapy for the prevention of cardiovascular disease or dementia [*see Warnings and Precautions (5.1, 5.3), and Clinical Studies (14.5, 14.6)*].

**Breast Cancer**

The WHI estrogen plus progestin substudy demonstrated an increased risk of invasive breast cancer [*see Warnings and Precautions (5.2) and Clinical Studies (14.5)*].

Only daily oral 0.625 mg CE and 2.5 mg MPA were studied in the estrogen plus progestin substudy of the WHI. Therefore, the relevance of the WHI findings regarding adverse cardiovascular events, dementia and breast cancer to lower CE plus other MPA doses, other routes of administration, or other estrogen plus progestogen products is not known. Without such data, it is not possible to definitively exclude these risks or determine the extent of these risks for other products. Discuss with your patient the benefits and risks of estrogen plus progestogen therapy, taking into account her individual risk profile.

Prescribe estrogens with or without progestogens 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 progestogen to estrogen therapy has been shown to reduce the risk of endometrial

hyperplasia, which may be a precursor to endometrial cancer. Perform adequate diagnostic measures, including directed or random endometrial sampling when indicated, 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**

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 and 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)*].

Do not use estrogen-alone therapy for the prevention of cardiovascular disease or dementia [*see Warnings and Precautions (5.1, 5.3), and Clinical Studies (14.5, 14.6)*].

Only daily oral 0.625 mg CE was studied in the estrogen-alone substudy of the WHI. Therefore, the relevance of the WHI findings regarding adverse cardiovascular events and dementia to lower CE doses, other routes of administration, or other estrogen-alone products is not known. Without such data, it is not possible to definitively exclude these risks or determine the extent of these risks for other products. Discuss with your patient the benefits and risks of estrogen-alone therapy, taking into account her individual risk profile.

Prescribe estrogens with or without progestogens 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, first consider the use of non-estrogen medications. Consider estrogen therapy only for women at significant risk of osteoporosis.

## 2 DOSAGE AND ADMINISTRATION

Use estrogen, alone or in combination with a progestogen, at the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual woman. Re-evaluate postmenopausal women periodically as clinically appropriate to determine whether treatment is still necessary.

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

Take a single norethindrone acetate and ethinyl estradiol tablet, orally once daily.

### 2.2 Prevention of Postmenopausal Osteoporosis

Take a single norethindrone acetate and ethinyl estradiol tablet, orally once daily

## 3 DOSAGE FORMS AND STRENGTHS

The following two strengths of Norethindrone Acetate and Ethinyl Estradiol Tablets, USP are available:

### **Norethindrone Acetate and Ethinyl Estradiol Tablets, USP (0.5 mg/2.5 mcg):**

Each light pink to pink, round, flat-faced beveled edge, uncoated tablet contains 0.5 mg norethindrone acetate, USP and 2.5 mcg ethinyl estradiol, USP; debossed with 'D5' on one side and plain on the other side.

**Norethindrone Acetate and Ethinyl Estradiol Tablets, USP (1 mg/5 mcg):** Each white to off-white, round, flat-faced beveled edge, uncoated tablet contains 1 mg norethindrone acetate, USP and 5 mcg ethinyl estradiol, USP; debossed with 'D6' on one side and plain on the other side.

## 4 CONTRAINDICATIONS

Norethindrone acetate and ethinyl estradiol tablets are contraindicated in women with any of the following conditions:

- Undiagnosed abnormal genital bleeding [*see Warnings and Precautions (5.2)*].
- Breast cancer or a history of breast cancer [*see Warnings and Precautions (5.2)*].
- Estrogen-dependent neoplasia [*see Warnings and Precautions (5.2)*].
- Active DVT, PE or a history of these conditions [*see Warnings and Precautions (5.1)*].
- Active arterial thromboembolic disease (for example, stroke and MI), or a history of these conditions [*see Warnings and Precautions (5.1)*].
- Known anaphylactic reaction, angioedema, or hypersensitivity to norethindrone acetate and ethinyl estradiol tablets.
- Hepatic impairment or disease.
- Protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders.

## 5 WARNINGS AND PRECAUTIONS

## 5.1 Cardiovascular Disorders

Increased risk of PE, DVT, stroke, and MI are reported with estrogen plus progestin therapy. Increased risks of stroke and DVT are reported with estrogen-alone therapy. Immediately discontinue estrogen with or without progestogen therapy if any of these occur or are suspected.

Manage appropriately any 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).

### Stroke

The WHI estrogen plus progestin substudy reported a statistically significant increased risk of stroke 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 strokes 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> Immediately discontinue estrogen with or without progestogen therapy if a stroke occurs or is suspected.

The WHI estrogen-alone substudy, reported a statistically significant increased risk of stroke 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)*]. Immediately discontinue estrogen-alone therapy if a stroke occurs or is suspected.

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

The WHI estrogen plus progestin substudy reported an increased risk (not statistically significant) of coronary heart disease (CHD) events (defined as nonfatal MI, silent MI, or CHD death) in those 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)*].

The WHI estrogen-alone substudy reported no overall effect on CHD events 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, who were less than 10 years since menopause, suggest a reduction (not statistically significant) of CHD events in those women receiving CE (0.625 mg)-alone compared to placebo (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

The WHI estrogen plus progestin substudy reported a statistically significant 2-fold greater rate of VTE (DVT and PE) 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)*]. Immediately discontinue estrogen plus progestogen therapy if a VTE occurs or is suspected.

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)*]. Immediately discontinue estrogen-alone therapy if a VTE occurs or is suspected.

If feasible, discontinue estrogens 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

After a mean follow-up of 5.6 years, the WHI substudy of daily CE (0.625 mg) plus MPA (2.5 mg) reported an increased risk of invasive breast cancer in women who took daily CE plus MPA compared to placebo. 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 WHI substudy of daily CE (0.625 mg)-alone provided information about breast cancer in estrogen-alone users. 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 compared to placebo<sup>6</sup> [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. One large meta-analysis of prospective cohort studies reported increased risks that were dependent upon duration of use and could last up to >10 years after discontinuation of estrogen plus progestin therapy and estrogen-alone therapy. Extension of the WHI trials also demonstrated increased breast cancer risk associated with estrogen plus progestin therapy. 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. These studies have not generally 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 norethindrone acetate and ethinyl estradiol tablets.

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 progestogen 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 progestogen 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 CE plus MPA substudy of WHI reported that estrogen plus progestin increased the risk of ovarian cancer. After an average follow-up of 5.6 years, the relative risk for ovarian cancer for CE plus MPA versus placebo was 1.58 (95 percent CI, 0.77 to 3.24),

but it was not statistically significant. The absolute risk for CE plus MPA versus placebo was 4 versus 3 cases per 10,000 women-years.<sup>7</sup>

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

### **5.3 Probable Dementia**

In the WHI Memory Study (WHIMS) estrogen plus progestin ancillary study, 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, 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 Populations (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 2.6). 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 Populations (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. Discontinue estrogens, including norethindrone acetate and ethinyl estradiol tablets, if hypercalcemia occurs, and take appropriate measures to reduce the serum calcium level.

## **5.6 Visual Abnormalities**

Retinal vascular thrombosis has been reported in women receiving estrogens. Discontinue norethindrone acetate and ethinyl estradiol tablets pending examination if there is sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine. Permanently discontinue estrogens, including norethindrone acetate and ethinyl estradiol tablets, if examination reveals papilledema or retinal vascular lesions.

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

Studies of the addition of a progestogen 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 progestogens 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 Exacerbation of Hypertriglyceridemia**

In women with pre-existing hypertriglyceridemia, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis. Discontinue norethindrone acetate and ethinyl estradiol tablets if pancreatitis occurs.

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

Estrogens may be poorly metabolized in women with hepatic impairment. Exercise caution in any women with a history of cholestatic jaundice associated with past estrogen use or with pregnancy. In the case of recurrence of cholestatic jaundice, discontinue norethindrone acetate and ethinyl estradiol tablets.

## **5.11 Exacerbation of 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. Monitor thyroid function in these women during treatment with norethindrone acetate and ethinyl estradiol tablets to maintain their free thyroid hormone levels in an

acceptable range.

### **5.12 Fluid Retention**

Estrogens plus progestogens may cause some degree of fluid retention. Monitor any women with condition(s) that might predispose her to fluid retention, such as cardiac or renal impairment. Discontinue estrogen plus progestogen therapy, including norethindrone acetate and ethinyl estradiol tablets, with evidence of medically concerning fluid retention.

### **5.13 Hypocalcemia**

Estrogen-induced hypocalcemia may occur in women with hypoparathyroidism. Consider whether the benefits of estrogen therapy, including norethindrone acetate and ethinyl estradiol tablets, outweigh the risks in such women.

### **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.

### **5.15 Hereditary Angioedema**

Exogenous estrogens may exacerbate symptoms of angioedema in women with hereditary angioedema. Consider whether the benefits of estrogen therapy, including norethindrone acetate and ethinyl estradiol tablets, outweigh the risks in such women.

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

Estrogen therapy, including norethindrone acetate and ethinyl estradiol tablets, may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine, porphyria, systemic lupus erythematosus and hepatic hemangiomas. Consider whether the benefits of estrogen therapy outweigh the risks in women with such conditions.

### **5.17 Laboratory Tests**

Serum follicle stimulating hormone (FSH) and estradiol levels have not been shown to be useful in the management of postmenopausal women with 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. Norethindrone acetate and ethinyl estradiol tablets 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 women in controlled clinical studies of norethindrone acetate and ethinyl estradiol tablets are shown in Table 1.

**Table 1. Associated Adverse Reactions Reported by  $\geq 5$  Percent of Women by Body System\***

BODY SYSTEM/ Adverse Reaction	Number (Percent) of Subjects		
	Placebo	Norethindrone Acetate and Ethinyl Estradiol Tablets 0.5/2.5	Norethindrone Acetate and Ethinyl Estradiol Tablets 1/5
	N = 247	N = 244	N = 258
BODY AS A WHOLE	23 (12.8)	30 (16.9)	30 (15.7)
Edema -	10 (4)	12 (4.9)	11 (4.3)

Generalized	10 (4)	12 (4.9)	11 (4.5)
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)	20 (7.8)

\*The total number of women for each body system may be less than the number of women with AEs in that body system because a women 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 tablets. 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**

*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 and progestin 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 and progestins, 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 adverse reactions.

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.

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**

#### **Risk Summary**

Norethindrone acetate and ethinyl estradiol tablets are not indicated for use in pregnancy. There are no data with the use of norethindrone acetate and ethinyl estradiol tablets in pregnant women; however, epidemiologic studies and meta-analyses have not found an increased risk of genital or nongenital birth defects (including cardiac anomalies and limb-reduction defects) following exposure to combined (estrogens and progestins) product before conception or during early pregnancy.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

## **8.2 Lactation**

### Risk Summary

Estrogens plus progestogens are present in human milk and can reduce milk production in breast-feeding women. This reduction can occur at any time but is less likely to occur once breast-feeding is well-established. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for norethindrone acetate and ethinyl estradiol tablets and any potential adverse effects on the breastfed child from norethindrone acetate and ethinyl estradiol tablets or from the underlying maternal condition.

## **8.4 Pediatric Use**

Norethindrone acetate and ethinyl estradiol tablets are not indicated for use in pediatric patients. 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 tablets to determine whether those over 65 years of age differ from younger subjects in their response to norethindrone acetate and ethinyl estradiol tablets.

### *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)*].



## 10 OVERDOSAGE

Overdosage of estrogen plus progestogen 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 norethindrone acetate and ethinyl estradiol tablets therapy with institution of appropriate symptomatic care.

## 11 DESCRIPTION

Norethindrone Acetate and Ethinyl Estradiol Tablets, USP is a continuous dosage regimen of a progestin-estrogen combination for oral administration.

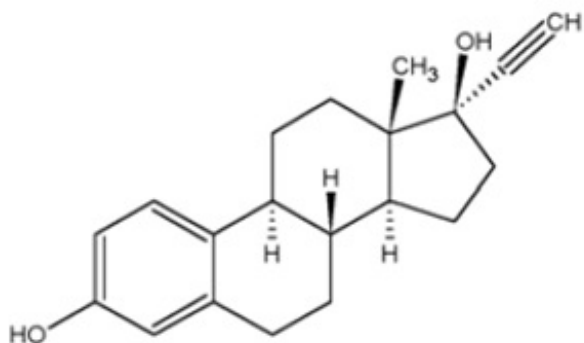
The following two strengths of Norethindrone Acetate and Ethinyl Estradiol Tablets, USP are available as:

Norethindrone Acetate and Ethinyl Estradiol Tablets USP (0.5 mg/2.5 mcg): Each light pink to pink, round, flat-faced beveled edge, uncoated tablet contains 0.5 mg norethindrone acetate, USP and 2.5 mcg ethinyl estradiol, USP.

Norethindrone Acetate and Ethinyl Estradiol Tablets USP (1 mg/5 mcg): Each white to off-white, round, flat-faced beveled edge, uncoated tablet contains 1 mg norethindrone acetate, USP and 5 mcg ethinyl estradiol, USP.

Each tablet also contains the following inactive ingredients: calcium stearate, cornstarch, lactose monohydrate, microcrystalline cellulose, povidone and vitamin E and talc. The 0.5 mg/2.5 mcg light pink to pink tablet also contains D&C red no. 30.

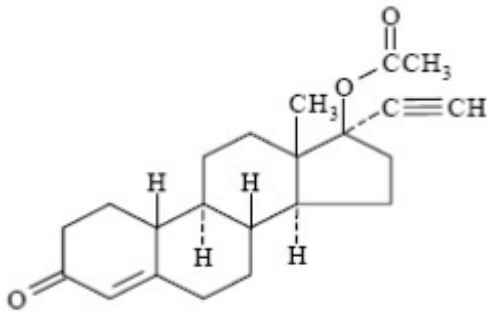
The structural formulas are as follows



Ethinyl Estradiol, USP [19-Nor-17 $\alpha$ -pregna-1,3,5(10)-trien-20-yne-3,17-diol]

Molecular Weight: 296.40

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



Norethindrone Acetate USP [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

Generally, a serum estrogen concentration does not predict an individual woman's therapeutic response to norethindrone acetate and ethinyl estradiol tablets nor her risk for adverse outcomes. Likewise, exposure comparisons across different estrogen products to infer efficacy or safety for the individual woman may not be valid.

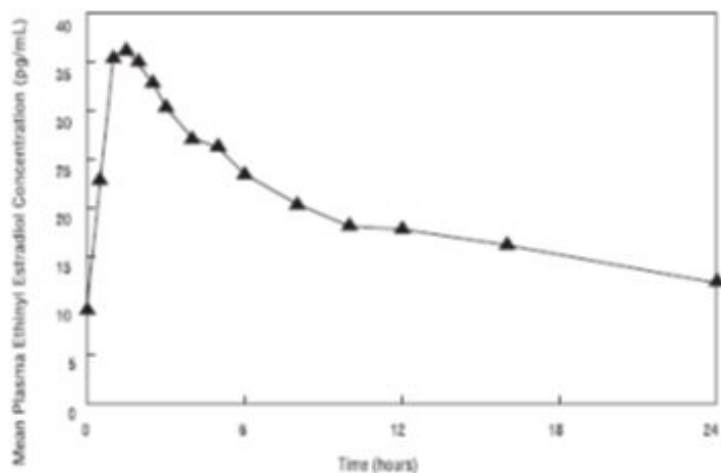
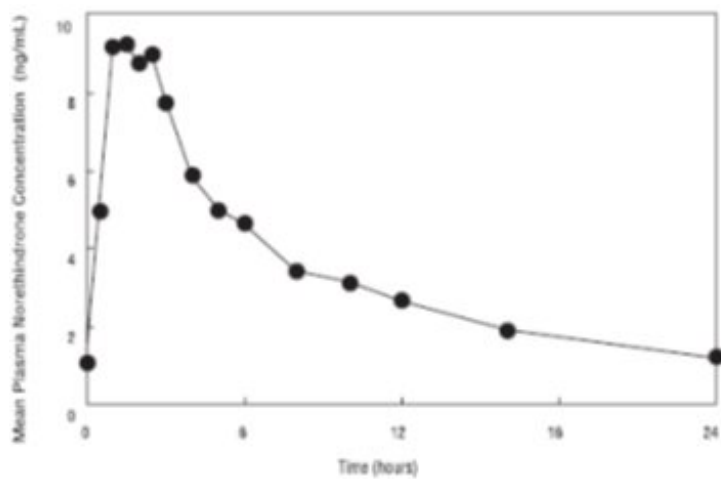
## 12.3 Pharmacokinetics

### 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 tablets 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 tablets was not characterized due to assay sensitivity limitations. However, the multiple-dose pharmacokinetics were studied at a dose of 1 mg NA/10 mcg EE in 18 post-menopausal 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 NA/5 mcg EE and 1/10 are slightly more than proportional to dose when compared to 0.5 mg NA/2.5 mcg EE 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 NA/EE 1 /10 tablet.

**Figure 1. Mean Steady-State (Day 87) Plasma Norethindrone and Ethinyl Estradiol Concentrations Following Continuous Oral Administration of 1 mg NA/10 mcg EE Tablets**



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

	$C_{max}$	$t_{max}$	AUC (0 to 24)	CL/F	$t_{1/2}$
<b>NORETHINDRONE</b>	ng/mL	hr	ng•hr/mL	mL/min	hr
Day 1	6 (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	2.2	339	ND†	ND†

Day 1	(13.7)	(1)	(113)	ND <sup>†</sup>	ND <sup>†</sup>
Day 87	38.3 (11.9)	1.8 (0.7)	471 (132)	383 (119)	23.9 (7.1)

<sup>†</sup>C<sub>max</sub> = Maximum plasma concentration; t<sub>max</sub> = time of C<sub>max</sub>; AUC (0 to 24) = Area under the plasma concentration-time curve over the dosing interval; and CL/F = Apparent oral clearance;

t<sub>1/2</sub> = Elimination half-life

‡ND = Not determined

Based on a population pharmacokinetic analysis, average steady-state concentrations (C<sub>ss</sub>) 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<sub>ss</sub> 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 NA/10 mcg EE tablets are approximately 13 hours and 24 hours, respectively.

## **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 in Postmenopausal Women**

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, women had 12 hot flushes per day upon study entry.

A total of 66 women were randomized to receive norethindrone acetate and ethinyl estradiol tablets 1/5 and 66 women were randomized to the placebo group. Norethindrone acetate and ethinyl estradiol tablets 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 tablets 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**

<b>Visit</b>	<b>Placebo (N = 66)</b>	<b>Norethindrone Acetate and Ethinyl Estradiol Tablets 0.5 /2.5</b>	<b>Norethindrone Acetate and Ethinyl Estradiol Tablets 1 /5 (N = 66)</b>

		<b>(N = 67)</b>	
<b>Baseline [1]</b>			
Mean (SD)	76.5 (21.4)	77.6 (26.5)	70 (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 (26.6)	-47.4 <sup>è</sup> (26.1)	-49.6 <sup>è</sup> (22.1)
p-Value vs. Placebo (95 percent CI) [2]		0.041 (-20, -1)	<0.001 (-22, -6)
<b>Week 12</b>			
Mean (SD)	31.1 (27)	13.8 (20.4)	11.3 (18.9)
Mean Change from Baseline (SD)	-45.3 (30.2)	-63.8 <sup>è</sup> (27.5)	-58.7 <sup>è</sup> (23.1)
p-Value vs. Placebo (95 percent CI) [2]		<0.001 (-27, -7)	<0.001 (-25, -5)

<sup>è</sup> 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 tablets) 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**

<b>Visit</b>	<b>Placebo (N = 66)</b>	<b>Norethindrone Acetate and Ethinyl Estradiol Tablets 0.5 /2.5 (N = 67)</b>	<b>Norethindrone Acetate and Ethinyl Estradiol Tablets 1 /5 (N = 66)</b>
<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 <sup>¥</sup> (1.06)
p-Value vs Placebo (95 percent CI) [2]	-	0.130 (-0.3, 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)	-0.8 <sup>‡</sup> (0.94)	-1.24 <sup>‡</sup> (1.07)
p-Value vs Placebo (95 percent CI) [2]	-	0.041 (-0.4, -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 <sup>‡</sup> (1.08)	-1.45 <sup>‡</sup> (1.19)
p-Value vs Placebo (95 percent CI) [2]	-	0.002 (-0.9, -0.2)	<0.001 (-1.4, -0.3)

<sup>‡</sup> 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 women (1 in Placebo and 1 in norethindrone acetate and ethinyl estradiol tablets) 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 tablets 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 NA/1 mcg ethinyl estradiol (NA/EE 0.2 /1), 0.5 mg NA/2.5 mcg EE (NA/EE 0.5 /2.5), norethindrone acetate and ethinyl estradiol tablets 1/5 and 1 mg NA/10 mcg EE (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 tablets 1/5, 136 to NA/EE 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 tablets 1/5, 136 NA/EE 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 tablets 1/5 and appropriate comparators are shown in Table 5.

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



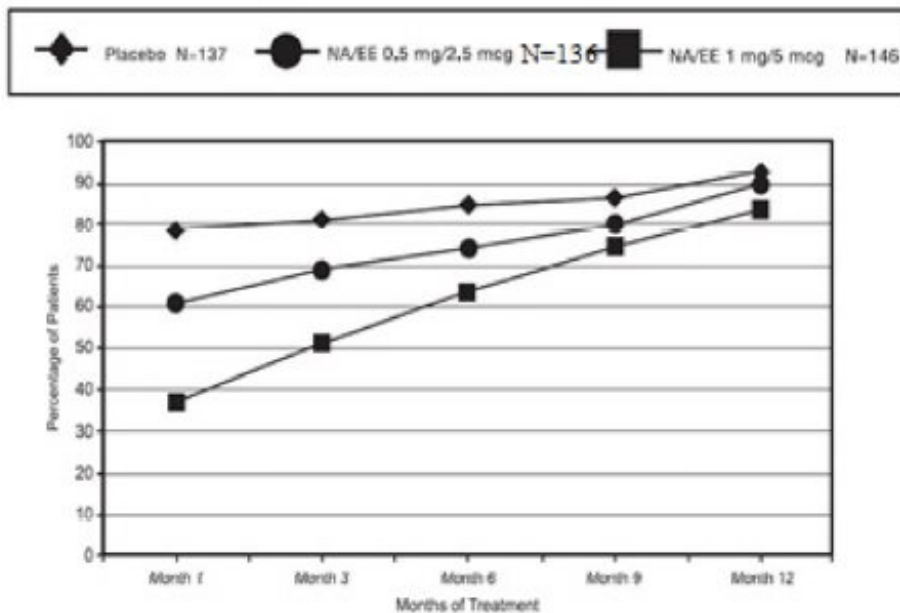
Endometrial Status	Placebo	Norethindrone Acetate and Ethinyl Estradiol Tablets		EE Alone	
		0.5/2.5	1/5	2.5 mcg	5 mcg
<b>Number of Patients Biopsied at Baseline</b>	N = 134	N = 136	N = 143	N = 137	N = 139
<b>MONTH 12 (Percent Patients)</b>					
Patients Biopsied (percent)	113 (84)	103 (74)	110 (77)	100 (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 *	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 *	1	0	0	0	2

\*All patients with endometrial hyperplasia were carried forward for all time points.

### 14.3 Effects on Uterine Bleeding or Spotting in Postmenopausal Women

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

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

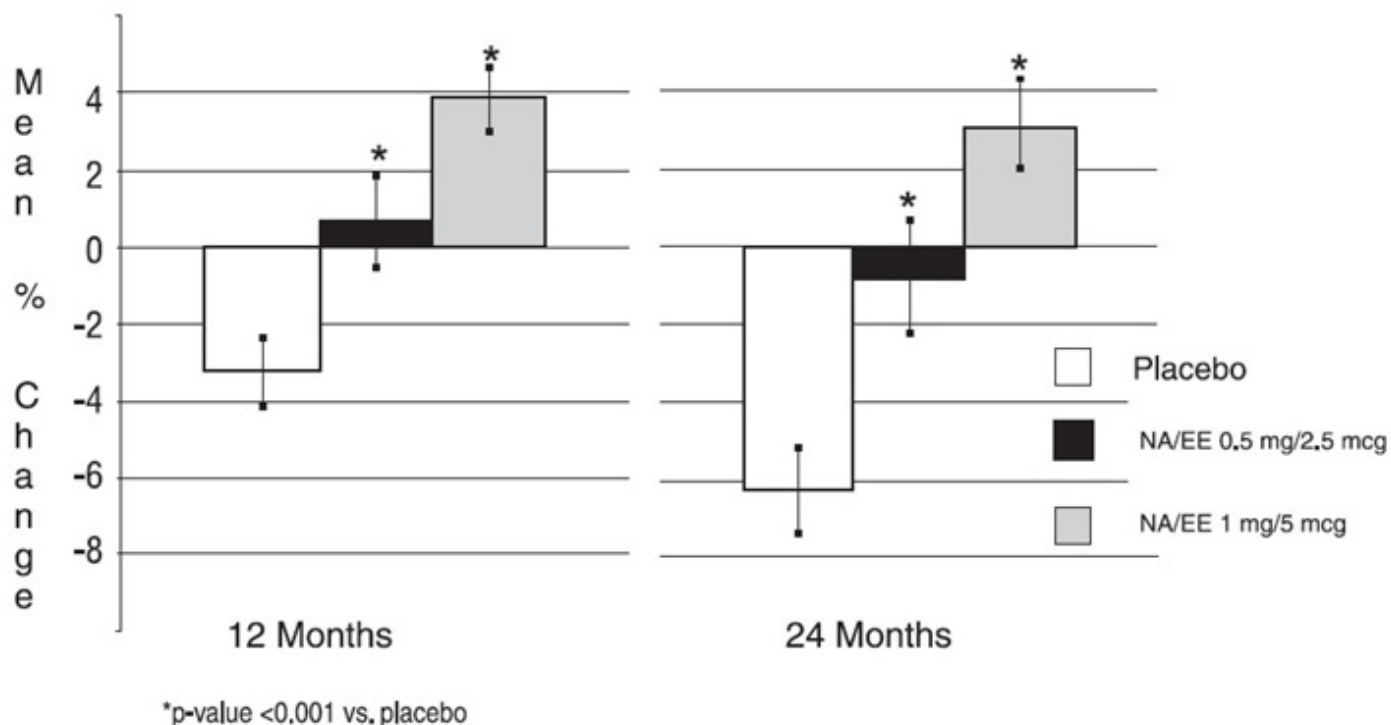


#### 14.4 Effect on Bone Mineral Density in Postmenopausal Women

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 non-osteoporotic bone mineral densities were randomized (1:1:1) to norethindrone acetate and ethinyl estradiol tablets 1/5, NA/EE 0.5/2.5 or placebo. Approximately 75 percent of the women in each group completed the two-year study. All women 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 tablets 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 tablets 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>¶</sup> #<sup>†</sup>**

Event	Relative Risk CE/MPA vs. Placebo (95 percent nCI <sup>β</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 to 1.63)</i>	<i>31</i>	<i>25</i>
<i>CHD death</i>	<i>1.10 (0.7 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 1.9)</i>	<i>26</i>	<i>18</i>
Deep vein thrombosis <sup>à</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>é</sup>	1.24 (1.01 to 1.54)	41	33
Colorectal cancer	0.61 (0.42 to 0.87)	10	16
Endometrial cancer <sup>à</sup>	0.81 (0.48 to 1.36)	6	7
Cervical cancer <sup>à</sup>	1.44 (0.47 to 4.42)	2	1
Hip fracture	0.67 (0.47 to 0.96)	11	16

Vertebral fractures <sup>à</sup>	0.65 (0.46 to 0.92)	11	17
Lower arm/wrist fractures <sup>à</sup>	0.71 (0.59 to 0.85)	44	62
Total fractures <sup>à</sup>	0.76 (0.69 to 0.83)	152	199
Overall Mortality <sup>β</sup> <sup>δ</sup>	1 (0.83 to 1.19)	52	52
Global Index <sup>ø</sup>	1.13 (1.02 to 1.25)	184	165

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

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

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

<sup>à</sup> Not included in "global index".

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

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

<sup>ø</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**

Event	Relative Risk CE vs. Placebo (95 percent nCI <sup>CE</sup> )	CE N = 5,310	Placebo n = 5,429
		Absolute Risk per 10,000 Women-Years	
CHD events <sup>ce</sup>	0.95 (0.78 to 1.16)	54	57
<i>Non-fatal MI</i> <sup>ce</sup>	<i>0.91 (0.73 to 1.14)</i>	40	42
<i>CHD death</i> <sup>ce</sup>	<i>1.01 (0.71 to 1.43)</i>	16	16
All strokes <sup>ce</sup>	1.33 (1.05 to 1.68)	45	33
<i>Ischemic stroke</i> <sup>ce</sup>	<i>1.55 (1.19 to 2.01)</i>	38	25
Deep vein thrombosis <sup>ce</sup> <sup>Ⓓ</sup>	1.47 (1.06 to 2.06)	23	15
Pulmonary embolism <sup>ce</sup>	1.37 (0.90 to 2.07)	14	10
Invasive breast cancer <sup>ce</sup>	0.80 (0.62 to 1.04)	28	34
Colorectal cancer*	1.08 (0.75 to 1.55)	17	16
Hip fracture <sup>ce</sup>	0.65 (0.45 to 0.94)	12	19
Vertebral fractures <sup>ce</sup> <sup>Ⓓ</sup>	0.64 (0.44 to 0.93)	11	18
Lower arm/wrist fractures <sup>ce</sup> <sup>Ⓓ</sup>	0.58 (0.47 to 0.72)	35	59
Total fractures <sup>ce</sup> <sup>Ⓓ</sup>	0.71 (0.64 to 0.8)	144	197
Deaths due to other causes* <sup>†</sup>	1.08 (0.88 to 1.32)	53	50
Overall Mortality <sup>ce</sup> <sup>Ⓓ</sup>	1.04 (0.88 to 1.22)	79	75
Global Index <sup>‡</sup>	1.02(0.92 to 1.13)	206	201

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

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

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

<sup>Ⓓ</sup> Not included in "global index".

\* Results are based on an average follow-up of 6.8 years.

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

<sup>‡</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 and older (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 2.6). 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

Norethindrone Acetate and Ethinyl Estradiol Tablets, USP are available in the following strengths and package sizes:

Norethindrone Acetate and Ethinyl Estradiol Tablets, USP 0.5 mg/2.5 mcg, are light pink to pink, round, flat-faced, beveled edge, uncoated, tablets debossed with "D5" on one side and plain on the other side. Each tablet contains 0.5 mg norethindrone acetate, USP and 2.5 mcg ethinyl estradiol, USP and are available as:

NDC 68462-656-90 Bottle of 90 Tablets

NDC 68462-656-29 1 carton containing 3 individual foil pouches. Each pouch contains 1 blister of 28 tablets

Norethindrone Acetate and Ethinyl Estradiol Tablets, USP 1 mg/5 mcg are white to off-



white, round, flat-faced, beveled edge, uncoated tablets debossed with “D6” on one side plain on the other side. Each tablet contains 1 mg norethindrone acetate, USP and 5 mcg ethinyl estradiol, USP and are available as:

NDC 68462-657-90 Bottle of 90 Tablets

NDC 68462-657-29 1 carton containing 3 individual foil pouches. Each pouch contains 1 blister of 28 tablets

## **16.2 Storage and Handling**

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature].

Keep norethindrone acetate and ethinyl estradiol tablets out of the reach of children.

## **17 PATIENT COUNSELING INFORMATION**

Advise women to read the FDA-approved patient labeling (Patient Information)

### **Vaginal Bleeding**

Inform postmenopausal women to report any vaginal bleeding to their healthcare provider as soon as possible [see *Warnings and Precautions (5.2)*].

### **Possible Serious Adverse Reactions with Estrogen Plus Progestogen Therapy**

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

### **Possible Common Adverse Reactions with Estrogen Plus Progestogen Therapy**

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

Manufactured by:

**Glenmark Pharmaceuticals Limited**

Colvale-Bardez, Goa 403513, India

Manufactured for:



**Glenmark Pharmaceuticals Inc., USA**

Mahwah, NJ 07430

Questions? 1 (888) 721-7115

[www.glenmarkpharma-us.com](http://www.glenmarkpharma-us.com)

November 2023

## **PATIENT INFORMATION**

### **Norethindrone Acetate and Ethinyl Estradiol (nor-eth-IN-drone ASS-uh-TATE and ETH in il es tra DYE ole) Tablets, USP**

#### **0.5 mg/2.5 mcg and 1 mg/5 mcg**

Read this Patient Information before you start using norethindrone acetate and ethinyl estradiol tablets 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 norethindrone acetate and ethinyl estradiol tablets (a combination of estrogen and progestogen)?**

- Do not use estrogens with or without progestogens to prevent heart disease, heart attacks, strokes or dementia (decline of brain function).
- Using estrogens with progestogens may increase your chances of getting heart attack, strokes, breast cancer, or blood clots.
- Using estrogens with progestogens may increase your chance of getting dementia, based on a study of women 65 years of age and older.
- Using estrogen-alone may increase your chance of getting cancer of the uterus (womb).
- Do not use estrogen-alone to prevent heart disease, heart attacks, strokes or dementia (decline of brain function).
- 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 and older.
- Only one estrogen with progestogen product and dose have been shown to increase your chances of getting heart attacks, strokes, breast cancer, blood clots, and dementia. Only one estrogen-alone product and dose have been shown to increase your chances of getting strokes, blood clots, and dementia. Because other products and doses have not been studied in the same way, it is not known how the use of norethindrone acetate and ethinyl estradiol tablets will affect your chances of these conditions. You and your healthcare provider should talk regularly about whether you still need treatment with norethindrone acetate and ethinyl estradiol tablets.

#### **What are norethindrone acetate and ethinyl estradiol tablets?**

Norethindrone acetate and ethinyl estradiol tablets are a prescription medicine that contains two kinds of hormones, an estrogen and a progestogen.

#### **What are norethindrone acetate and ethinyl estradiol tablets used for?**

Norethindrone acetate and ethinyl estradiol tablets are 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 norethindrone acetate and ethinyl estradiol tablets 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 norethindrone acetate and ethinyl estradiol tablets.

### **Who should not use norethindrone acetate and ethinyl estradiol tablets?**

**Do not use norethindrone acetate and ethinyl estradiol tablets if you have had your uterus (womb) removed (hysterectomy).**

Norethindrone acetate and ethinyl estradiol tablets contain a progestogen to decrease the chance of getting cancer of the uterus (womb). If you do not have a uterus, you do not need a progestogen and you should not take norethindrone acetate and ethinyl estradiol tablets.

### **Do not start using norethindrone acetate and ethinyl estradiol tablets 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 been diagnosed with a bleeding disorder.**
- **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 (womb). If you have or have had cancer, talk with your healthcare provider about whether you should take norethindrone acetate and ethinyl estradiol tablets.

- **had a stroke or heart attack**
- **currently have or have had blood clots**
- **currently have or have had liver problems**
- **are allergic to norethindrone acetate and ethinyl estradiol tablets or any of its ingredients.**

See the list of ingredients in norethindrone acetate and ethinyl estradiol tablets at the end of this leaflet.

**Before you use norethindrone acetate and ethinyl estradiol tablets, tell your healthcare provider about all of your medical conditions, including 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 conditionsthat may become worse while you are using norethindrone acetate and ethinyl estradiol tablets.**

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 using norethindrone acetate and ethinyl estradiol tablets.

- **are pregnant or think you may be pregnant.**

Norethindrone acetate and ethinyl estradiol tablets is not for pregnant women.

- **are breastfeeding**

The hormones in norethindrone acetate and ethinyl estradiol tablets can pass into your breast milk.

**Tell your healthcare provider about all the medicines you take,** including prescription and over-the-counter medicines, vitamins, and herbal supplements. Some medicines may affect how norethindrone acetate and ethinyl estradiol tablets works. Some other medicines and food products may increase or decrease the concentrations of the hormones in norethindrone acetate and ethinyl estradiol tablets in the blood. Norethindrone acetate and ethinyl estradiol tablets 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 use norethindrone acetate and ethinyl estradiol tablets?**

- Take norethindrone acetate and ethinyl estradiol tablets exactly as your healthcare provider tells you to take it.
- Take 1 norethindrone acetate and ethinyl estradiol 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 norethindrone acetate and ethinyl estradiol tablets.

### **What are the possible side effects of norethindrone acetate and ethinyl estradiol tablets?**

**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
- Breast cancer
- Cancer of the lining of the uterus (womb)
- Cancer of the ovary
- Dementia

- Gallbladder disease
- High or low blood calcium levels
- Changes in vision
- High blood pressure
- High levels of fat in your blood
- Liver problems
- Changes in your thyroid hormone levels
- Swelling or fluid retention
- Cancer changes of endometriosis
- Enlargement of benign tumors of the uterus (“fibroids”)
- Worsening swelling of face or tongue (angioedema) in women who have a history of angioedema
- Changes in laboratory test results such as bleeding time and high blood sugar levels

**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

**Common side effects of norethindrone acetate and ethinyl estradiol tablets 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 norethindrone acetate and ethinyl estradiol tablets. 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 Glenmark Pharmaceuticals Inc., USA at 1 (888) 721-7115 or FDA at 1-800-FDA-1088.

**What can I do to lower my chances of a serious side effect with norethindrone acetate and ethinyl estradiol tablets?**

- Talk with your healthcare provider regularly about whether you should continue using norethindrone acetate and ethinyl estradiol tablets.
- If you have a uterus, talk with your healthcare provider about whether norethindrone acetate and ethinyl estradiol tablet is right for you.
- In general, the addition of a progestogen is 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 get vaginal bleeding while using norethindrone acetate and ethinyl estradiol tablets.
- 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 norethindrone acetate and ethinyl estradiol tablets?**

Store norethindrone acetate and ethinyl estradiol tablets at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

### **Keep norethindrone acetate and ethinyl estradiol tablets out of the reach of children.**

### **General information about the safe and effective use of norethindrone acetate and ethinyl estradiol tablets.**

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use norethindrone acetate and ethinyl estradiol tablets for conditions for which it was not prescribed. Do not give norethindrone acetate and ethinyl estradiol tablets to other people, even if they have the same symptoms you have. It may harm them.

You can ask your pharmacist or healthcare provider for information about norethindrone acetate and ethinyl estradiol tablets that is written for health professionals.

For more information about norethindrone acetate and ethinyl estradiol tablets, call Glenmark Pharmaceuticals Inc., USA at 1 (888) 721-7115.

### **What are the ingredients in norethindrone acetate and ethinyl estradiol tablets?**

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

**Inactive Ingredients:** calcium stearate, cornstarch, lactose monohydrate, microcrystalline cellulose, povidone and vitamin E and talc. The 0.5 mg/2.5 mcg light pink to pink tablets also contain D&C red no. 30.

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

Manufactured by:

**Glenmark Pharmaceuticals Limited**

Colvale-Bardez, Goa 403513, India

Manufactured for:



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November 2023

### PRINCIPAL DISPLAY PANEL



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## NORETHINDRONE ACETATE AND ETHINYL ESTRADIOL

norethindrone acetate and ethinyl estradiol tablet

### Product Information

<b>Product Type</b>	HUMAN PRESCRIPTION DRUG	<b>Item Code (Source)</b>	NDC:68462-656
<b>Route of Administration</b>	ORAL		

### Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
<b>NORETHINDRONE ACETATE</b> (UNII: 9S44LIC7OJ) (NORETHINDRONE - UNII:T18F433X4S)	NORETHINDRONE ACETATE	0.5 mg
<b>ETHINYL ESTRADIOL</b> (UNII: 423D2T571U) (ETHINYL ESTRADIOL - UNII:423D2T571U)	ETHINYL ESTRADIOL	2.5 ug



## Inactive Ingredients

Ingredient Name	Strength
<b>CALCIUM STEARATE</b> (UNII: 776XM7047L)	
<b>STARCH, CORN</b> (UNII: O8232NY35J)	
<b>ISOPROPYL ALCOHOL</b> (UNII: ND2M416302)	
<b>LACTOSE MONOHYDRATE</b> (UNII: EWQ57Q8I5X)	
<b>MICROCRYSTALLINE CELLULOSE</b> (UNII: OP1R32D61U)	
<b>POVIDONE K30</b> (UNII: U725QWY32X)	
<b>.ALPHA.-TOCOPHEROL</b> (UNII: H4N855PNZ1)	
<b>D&amp;C RED NO. 30</b> (UNII: 2S42T2808B)	
<b>TALC</b> (UNII: 7SEV7J4R1U)	

## Product Characteristics

<b>Color</b>	PINK (light pink to pink)	<b>Score</b>	no score
<b>Shape</b>	ROUND (uncoated, flat-faced, beveled-edge)	<b>Size</b>	6mm
<b>Flavor</b>		<b>Imprint Code</b>	D5
<b>Contains</b>			

## Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:68462-656-90	90 in 1 BOTTLE; Type 0: Not a Combination Product	04/02/2015	
2	NDC:68462-656-29	3 in 1 CARTON	04/02/2015	
2		1 in 1 POUCH		
2		28 in 1 BLISTER PACK; Type 0: Not a Combination Product		

## Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA203038	04/02/2015	

## NORETHINDRONE ACETATE AND ETHINYL ESTRADIOL

norethindrone acetate and ethinyl estradiol tablet

### Product Information

<b>Product Type</b>	HUMAN PRESCRIPTION DRUG	<b>Item Code (Source)</b>	NDC:68462-657
<b>Route of Administration</b>	ORAL		

### Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
<b>NORETHINDRONE ACETATE</b> (UNII: 9S44LIC7OJ) (NORETHINDRONE - UNII:T18F433X4S)	NORETHINDRONE ACETATE	1 mg
<b>ETHINYL ESTRADIOL</b> (UNII: 423D2T571U) (ETHINYL ESTRADIOL - UNII:423D2T571U)	ETHINYL ESTRADIOL	5 ug

### Inactive Ingredients

Ingredient Name	Strength
<b>CALCIUM STEARATE</b> (UNII: 776XM7047L)	
<b>STARCH, CORN</b> (UNII: O8232NY3SJ)	
<b>ISOPROPYL ALCOHOL</b> (UNII: ND2M416302)	
<b>LACTOSE MONOHYDRATE</b> (UNII: EWQ57Q8I5X)	
<b>MICROCRYSTALLINE CELLULOSE</b> (UNII: OP1R32D61U)	
<b>POVIDONE K30</b> (UNII: U725QWY32X)	
<b>.ALPHA.-TOCOPHEROL</b> (UNII: H4N855PNZ1)	
<b>TALC</b> (UNII: 7SEV7J4R1U)	

### Product Characteristics

<b>Color</b>	WHITE (white to off-white)	<b>Score</b>	no score
<b>Shape</b>	ROUND (uncoated, flat-faced, beveled-edge)	<b>Size</b>	6mm
<b>Flavor</b>		<b>Imprint Code</b>	D6
<b>Contains</b>			

### Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:68462-657-90	90 in 1 BOTTLE; Type 0: Not a Combination Product	04/02/2015	
2	NDC:68462-657-29	3 in 1 CARTON	04/02/2015	
2		1 in 1 POUCH		
2		28 in 1 BLISTER PACK; Type 0: Not a Combination Product		

### Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA203038	04/02/2015	

**Labeler** - Glenmark Pharmaceuticals Inc., USA (130597813)

### Establishment

Name	Address	ID/FEI	Business Operations
Glenmark Pharmaceuticals		677218665	ANALYSIS(68462-656, 68462-657) , MANUFACTURE(68462-656,

Limited

077510003 68462-657)

Revised: 11/2023

Glenmark Pharmaceuticals Inc., USA