

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

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

CENESTIN® (synthetic conjugated estrogens, A) Tablets, for oral use  
Initial U.S. Approval: 1999

**WARNING: ENDOMETRIAL CANCER, CARDIOVASCULAR DISORDERS, PROBABLE DEMENTIA and BREAST CANCER**  
See full prescribing information for complete boxed warning.

**Estrogen-Alone Therapy**

- There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens (5.2)
- Do not use estrogen-alone therapy for the prevention of cardiovascular disease or dementia (5.1, 5.3)
- The Women’s Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT) (5.1)
- The WHI Memory Study (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)

**Estrogen Plus Progestin Therapy**

- Do not use estrogen plus progestin therapy for the prevention of cardiovascular disease or dementia (5.1, 5.3)
- The WHI estrogen plus progestin substudy reported increased risks of DVT, pulmonary embolism (PE), stroke and myocardial infarction (MI) (5.1)
- The WHI estrogen plus progestin study reported increased risks of invasive breast cancer (5.2)
- The 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)

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

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

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

CENESTIN is a mixture of estrogens indicated for:

- Treatment of Moderate to Severe Vasomotor Symptoms due to Menopause (1.1).
  - Treatment of Moderate to Severe Symptoms of Vulvar and Vaginal Atrophy due to Menopause (1.2).
- Limitation of Use  
When prescribing solely for the treatment of moderate to severe symptoms of vulvar and vaginal atrophy, first consider the use of topical vaginal products.

-----DOSAGE AND ADMINISTRATION-----

- Start therapy with CENESTIN 0.45 mg once daily for the Treatment of Moderate to Severe Vasomotor Symptoms due to Menopause. Dosage adjustment should be guided by the clinical response (2.1).

- Start therapy with CENESTIN 0.3 mg once daily for the Treatment of Moderate to Severe Symptoms of Vulvar and Vaginal Atrophy due to Menopause (2.2).

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

- Tablet: 0.3 mg/day, 0.45 mg/day, 0.625 mg/day, 0.9 mg/day, and 1.25 mg/day.

-----CONTRAINDICATIONS-----

- Undiagnosed abnormal genital bleeding (4)
- Breast cancer or a history of cancer of the breast (4, 5.2)
- Estrogen-dependent neoplasia (4, 5.2)
- Active DVT, PE, or a history of these conditions (4, 5.1)
- Active arterial thromboembolic disease (for example, stroke and MI), or a history of these conditions (4, 5.1)
- Known anaphylactic reaction or angioedema or hypersensitivity to CENESTIN (4)
- Hepatic impairment or disease (4, 5.10)
- Protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders (4)

-----WARNINGS AND PRECAUTIONS-----

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

-----ADVERSE REACTIONS-----

The most common adverse reactions (> 10%) with CENESTIN are: headache, paresthesia, breast pain, abdominal pain, endometrial thickening, metrorrhagia, dizziness, pain, leg cramps, dyspepsia, leukorrhea, vaginitis and nausea (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Aspen Pharma USA Inc at +1-201-406-7955 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

-----DRUG INTERACTIONS-----

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

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

Revised: 11/2023

**FULL PRESCRIBING INFORMATION: CONTENTS\***

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

**1 INDICATIONS AND USAGE**

1.1 Treatment of Moderate to Severe Vasomotor Symptoms due to Menopause

1.2 Treatment of Moderate to Severe Symptoms of Vulvar and Vaginal Atrophy due to Menopause

**2 DOSAGE AND ADMINISTRATION**

2.1 Treatment of Moderate to Severe Vasomotor Symptoms due to Menopause

2.2 Treatment of Moderate to Severe Symptoms of Vulvar and Vaginal Atrophy due to Menopause

**3 DOSAGE FORMS AND STRENGTHS**

**4 CONTRAINDICATIONS**

**5 WARNINGS AND PRECAUTIONS**

5.1 Cardiovascular Disorders

5.2 Malignant Neoplasms

5.3 Probable Dementia

5.4 Gallbladder Disease

5.5 Hypercalcemia

5.6 Visual Abnormalities

5.7 Addition of a Progestin when a Woman has not had a Hysterectomy

5.8 Elevated Blood Pressure

5.9 Exacerbation of Hypertriglyceridemia

5.10 Hepatic Impairment and/or 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 Post Marketing Experience

**7 DRUG INTERACTIONS**

**8 USE IN SPECIFIC POPULATIONS**

8.1 Pregnancy

8.2 Lactation

8.4 Pediatric Use

8.5	Geriatric Use	14.4	Women's Health Initiative Memory Study
<b>10</b>	<b>OVERDOSAGE</b>	<b>15</b>	<b>REFERENCES</b>
<b>11</b>	<b>DESCRIPTION</b>	<b>16</b>	<b>HOW SUPPLIED/STORAGE AND HANDLING</b>
<b>12</b>	<b>CLINICAL PHARMACOLOGY</b>	16.1	How Supplied
12.1	Mechanism of Action	16.2	Storage and Handling
12.2	Pharmacodynamics	<b>17</b>	<b>PATIENT COUNSELING INFORMATION</b>
12.3	Pharmacokinetics		
<b>13</b>	<b>NONCLINICAL TOXICOLOGY</b>		
13.1	Carcinogenesis, Mutagenesis, Impairment of Fertility		
<b>14</b>	<b>CLINICAL STUDIES</b>		
14.1	Effects on Vasomotor Symptoms in Postmenopausal Women		
14.2	Effects on Vulvar and Vaginal Atrophy in Postmenopausal Women		
14.3	Women's Health Initiative Studies		

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

## FULL PRESCRIBING INFORMATION

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

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

##### **Endometrial Cancer**

There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. 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**

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 (14.3, 14.4)*].

The Women's Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT) in postmenopausal women (50 to 79 years of age) during 7.1 years of treatment with daily oral conjugated estrogens (CE) [0.625 mg]-alone, relative to placebo [see *Warnings and Precautions (5.1)*, and *Clinical Studies (14.3)*].

The WHI Memory Study (WHIMS) estrogen-alone ancillary study of the WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 5.2 years of treatment with daily CE (0.625 mg)-alone, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women [see *Warnings and Precautions (5.3)*, *Use in Specific Populations (8.5)*, and *Clinical Studies (14.4)*].

Only daily oral 0.625 mg CE was studied in the estrogen-alone substudy of 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 progestins at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

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

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

Do not use estrogen plus progestin therapy for the prevention of cardiovascular disease or dementia [see *Warnings and Precautions (5.1, 5.3)*, and *Clinical Studies (14.3, 14.4)*].

The WHI estrogen plus progestin substudy reported increased risks of DVT, pulmonary embolism (PE), stroke and myocardial infarction (MI) in postmenopausal women (50 to 79 years of age) during 5.6 years of treatment with daily oral CE (0.625 mg) combined with medroxyprogesterone acetate (MPA) [2.5 mg], relative to placebo [see *Warnings and Precautions (5.1)*, and *Clinical Studies (14.3)*].

The WHIMS estrogen plus progestin ancillary study of the WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with daily CE (0.625 mg) combined with MPA (2.5 mg), relative to placebo. It is unknown whether this finding applies to younger postmenopausal women [see *Warnings and Precautions (5.3)*, *Use in Specific Populations (8.5)*, and *Clinical Studies (14.4)*].

#### **Breast Cancer**

The WHI estrogen plus progestin substudy also demonstrated an increased risk of invasive breast cancer [see *Warnings and Precautions (5.2)*, and *Clinical Studies (14.3)*].

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 MPA doses, other routes of administration, or other estrogen plus progestin 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 progestin therapy, taking into account her individual risk profile.

Prescribe estrogens with or without progestins 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 Treatment of Moderate to Severe Symptoms of Vulvar and Vaginal Atrophy due to Menopause**

#### *Limitation of Use*

When prescribing solely for the treatment of moderate to severe symptoms of vulvar and vaginal atrophy, first consider the use of topical vaginal products.

## **2 DOSAGE AND ADMINISTRATION**

Generally, when estrogen is prescribed for a postmenopausal woman with a uterus, consider addition of a progestin to reduce the risk of endometrial cancer.

Generally, a woman without a uterus does not need to take a progestin in addition to her estrogen therapy. In some cases, however, hysterectomized women who have a history of endometriosis may need a progestin [see *Warnings and Precautions (5.2, 5.14)*].

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

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

Start therapy with CENESTIN 0.45 mg once daily. Make dosage adjustments based on the clinical response. Reevaluate postmenopausal women periodically as clinically appropriate to determine if treatment is still necessary. The lowest effective dose of CENESTIN for the treatment of moderate to severe vasomotor symptoms has not been determined.

## 2.2 Treatment of Moderate to Severe Symptoms of Vulvar and Vaginal Atrophy due to Menopause

Start therapy with CENESTIN 0.3 mg once daily.

### *Limitation of Use*

When prescribing solely for the treatment of moderate to severe symptoms of vulvar and vaginal atrophy, first consider the use of topical vaginal products.

## 3 DOSAGE FORMS AND STRENGTHS

CENESTIN (synthetic conjugated estrogens, A) Tablets are available as:

0.3 mg round, green, film-coated tablets debossed with the letters, **dp**, on one side and the number 41 on the other side.

0.45 mg round, orange, film-coated tablets debossed with the letters, **dp**, on one side and the number 46 on the other side.

0.625 mg round, red, film-coated tablets debossed with the letters, **dp**, on one side and the number 42 on the other side.

0.9 mg round, white, film-coated tablets debossed with the letters, **dp**, on one side and the number 43 on the other side.

1.25 mg round, blue, film-coated tablets debossed with the letters, **dp**, on one side and the number 44 on the other side.

## 4 CONTRAINDICATIONS

CENESTIN is 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 or angioedema or hypersensitivity to CENESTIN.
- 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 stroke and DVT are reported with estrogen-alone therapy. Increased risk of PE, DVT, stroke and MI are reported with estrogen plus progestin therapy. Immediately discontinue estrogen with or without progestin therapy if any of these occur or is 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-alone substudy reported a statistically significant increased risk of stroke in women 50 to 79 years of age receiving CE (0.625 mg)-alone compared to women in the same age group receiving placebo (45 versus 33 strokes per 10,000 women-years, respectively). The increase in risk was demonstrated in year 1 and persisted [see *Clinical Studies (14.3)*].

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>

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 (14.3)*]. The increase in risk was demonstrated after the first year and persisted.<sup>1</sup> Immediately discontinue estrogen plus progestin therapy if a stroke occurs or is suspected.

#### Coronary Heart Disease

The WHI estrogen-alone substudy reported no overall effect on coronary heart disease (CHD) events (defined as non-fatal MI, silent MI, or CHD death) in women receiving estrogen-alone compared to placebo<sup>2</sup> [see *Clinical Studies (14.3)*].

Subgroup analyses of women 50 to 59 years of age, who were less than 10 years since menopause, suggest a reduction (not statistically significant) in CHD events in those women receiving daily CE (0.625 mg)-alone compared to placebo (8 versus 16 per 10,000 women-years).<sup>1</sup>

The WHI estrogen plus progestin substudy reported an increased risk (not statistically significant) of CHD events in women receiving daily CE (0.625 mg) plus MPA (2.5 mg)

compared to women receiving placebo (41 versus 34 per 10,000 women-years).<sup>1</sup> An increase in relative risk was demonstrated in year 1, and a trend toward decreasing relative risk was reported in years 2 through 5 [see *Clinical Studies (14.3)*].

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 (0.625 mg) plus MPA (2.5 mg) group and the placebo group in HERS, HERS II, and overall.

#### Venous Thromboembolism

In the WHI estrogen-alone substudy, the risk of VTE (DVT and PE) 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>3</sup> [see *Clinical Studies (14.3)*]. Immediately discontinue estrogen-alone therapy if a VTE occurs or is suspected.

The WHI estrogen plus progestin substudy reported a statistically significant 2-fold greater rate of VTE was in women receiving 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>4</sup> [see *Clinical Studies (14.3)*]. Immediately discontinue estrogen plus progestin 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

### Endometrial Cancer

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 and this risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued.

Clinical surveillance of all women taking estrogen-alone or estrogen plus progestin therapy is important. Perform adequate diagnostic measures, including directed or random endometrial sampling when indicated, rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding with unknown etiology. There is no evidence that the use of natural estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent estrogen dose. Adding a progestin to postmenopausal estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.

#### Breast Cancer

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)<sup>5</sup> [see *Clinical Studies (14.3)*].

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% 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<sup>6</sup> [see *Clinical Studies (14.3)*]. 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>6</sup> [see *Clinical Studies (14.3)*].

Consistent with the WHI clinical trials, observational studies have also reported an increased risk of breast cancer with estrogen plus progestin therapy, and a smaller increase in the risk for breast cancer with 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.

### 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 CE plus MPA versus placebo was 1.58 (95 percent CI, 0.77-3.24) 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 1.27-1.48), 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-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, 0.83-2.66). 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 (14.4)*].

In the 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, 1.21-3.48). 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 (14.4)*].

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, 1.19-2.60). 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 Use in Specific Populations (8.5), and Clinical Studies (14.4)*].

#### **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 CENESTIN, 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 CENESTIN pending examination if there is sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine. Discontinue estrogens, including CENESTIN, if examination reveals papilledema or renal vascular lesions.

#### **5.7 Addition of a Progestin when a Woman has not had a Hysterectomy**

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

There are, however, possible risks that may be associated with the use of progestins with estrogens compared to estrogen-alone regimens. These include a possible 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 estrogens 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. Consider discontinuation of CENESTIN if pancreatitis occurs.

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

Estrogens may be poorly metabolized in women with hepatic impairment. Exercise caution in any woman with a history of cholestatic jaundice associated with past estrogen use or with pregnancy. In the case of recurrence of cholestatic jaundice, discontinue CENESTIN.

### **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 T4 and T3 serum concentrations in the normal range. Women dependent on thyroid hormone replacement therapy who are also receiving estrogens may require increased doses of their thyroid replacement therapy. Monitor thyroid function in these women during treatment with CENESTIN to maintain their free thyroid hormone levels in an acceptable range.

### **5.12 Fluid Retention**

Estrogens may cause some degree of fluid retention. Monitor any woman with a condition(s) that might predispose her to fluid retention, such as cardiac or renal impairment. Discontinue estrogen-alone therapy, including CENESTIN, 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 CENESTIN, 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. Consider the addition of a progestin for women known to have residual endometriosis post-hysterectomy.

### **5.15 Hereditary Angioedema**

Exogenous estrogens may exacerbate symptoms of angioedema in women with hereditary angioedema. Consider whether the benefits of estrogen therapy outweigh the risks in such women.

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

Estrogen therapy, including CENESTIN, 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 such women.

### **5.17 Laboratory Tests**

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

## 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 anti-factor 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), T4 levels (by column or by radioimmunoassay) or T3 levels by radioimmunoassay. T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 and free T3 concentrations are unaltered. 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. 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 HDL2 cholesterol subfraction concentrations, reduced low-density lipoprotein (LDL) cholesterol concentration, and increased triglyceride 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.

In a 12-week clinical trial that included 72 women treated with 0.625 mg and 2 x 0.625 mg CENESTIN and 48 women treated with placebo, adverse reactions that occurred at a rate of  $\geq 5$  percent are summarized in [Table 1](#).

**Table 1: Number (%) of Patients with Adverse Reactions with  $\geq 5$  Percent Occurrence Rate by Body System and Treatment Group**

<b>Body System Adverse Reaction</b>	<b>CENESTIN<sup>a</sup> 0.625 mg and 2 x 0.625 mg n=72</b>	<b>Placebo n=48</b>	<b>Total n=120</b>
Any Adverse Reaction (%)	68 (94)	43 (90)	111 (93)
<b>Body As A Whole</b>			
Abdominal Pain	20 (28)	11 (23)	31 (26)
Asthenia	24 (33)	20 (42)	44 (37)
Headache	49 (68)	32 (67)	81 (68)
Pain	8 (11)	9 (19)	17 (14)
<b>Digestive System</b>			
Dyspepsia	7 (10)	3 (6)	10 (8)
Flatulence	21 (29)	14 (29)	35 (29)
Nausea	13 (18)	9 (19)	22 (18)
Vomiting	5 (7)	1 (2)	6 (5)
<b>Metabolic and Nutritional</b>			
Peripheral Edema	7 (10)	6 (13)	13 (11)
<b>Nervous System</b>			
Depression	20 (28)	18 (38)	38 (32)
Dizziness	8 (11)	5 (10)	13 (11)
Insomnia	30 (42)	23 (48)	53 (44)
Leg Cramps	7 (10)	3 (6)	10 (8)
Paresthesia	24 (33)	15 (31)	39 (33)
Vertigo	12 (17)	12 (25)	24 (20)
<b>Urogenital System</b>	21 (29)	7 (15)	28 (23)
Breast Pain	4 (6)	3 (6)	7 (6)
Dysmenorrhea	10 (14)	3 (6)	13 (11)
Metrorrhagia	10 (14)	3 (6)	13 (11)

<sup>a</sup> Combined results for 0.625 mg and 2 x 0.625 mg CENESTIN Tablets

In a second 12-week clinical trial that included 52 women treated with 0.45 mg CENESTIN and 51 women treated with placebo, adverse reactions that occurred at a rate of >5 percent are summarized in Table 2.

**Table 2: Number (%) of Patients with a  $\geq$  5 Percent Occurrence Rate by Body System and Treatment Group**

<b>Body System and Term</b>	<b>CENESTIN 0.45 mg</b>	<b>Placebo</b>
Any Adverse Reaction (%)	40 (75.5%)	39 (76.5%)
Body As A Whole	20 (37.7%)	24 (47.1%)
Asthenia	6 (11.3%)	7 (13.7%)
Headache	6 (11.3%)	8 (15.7%)
Infection	1 (1.9%)	6 (11.8%)
Pain	6 (11.3%)	1 (2.0%)
Pain abdominal	5 (9.4%)	3 (5.9%)
Cardiovascular	5 (9.4%)	10 (19.6%)
Palpitations	3 (5.7%)	3 (5.9%)
Vasodilations	2 (3.8%)	4 (7.8%)
Digestive	8 (15.1%)	7 (13.7%)
Nausea	5 (9.4%)	2 (3.9%)
Metabolic and Nutritional	5 (9.4%)	3 (5.9%)
Weight increase	3 (5.7%)	2 (3.9%)
Musculoskeletal	5 (9.4%)	6 (11.8%)
Arthralgia	5 (9.4%)	5 (9.8%)
Myalgia	2 (3.8%)	6 (11.8%)
Neurological	15 (28.3%)	19 (37.3%)
Anxiety	3 (5.7%)	1 (2.0%)
Insomnia	3 (5.7%)	5 (9.8%)
Nervousness	2 (3.8%)	7 (13.7%)
Paresthesia	4 (7.5%)	3 (5.9%)
Vertigo	3 (5.7%)	3 (5.9%)
Respiratory	10 (18.9%)	6 (11.8%)
Rhinitis	3 (5.7%)	2 (3.9%)

<b>Body System and Term</b>	<b>CENESTIN 0.45 mg</b>	<b>Placebo</b>
Urogenital	19 (35.8%)	7 (13.7%)
Endometrial thickening	10 (18.9%)	4 (7.8%)
Vaginitis	4 (7.5%)	1 (2.0%)

If a subject experiences the same event more than once, the first occurrence is tabulated.

In a 16-week clinical trial that included 36 women treated with 0.3 mg CENESTIN and 34 women treated with placebo, adverse reactions that occurred at a rate of  $\geq 5$  percent are summarized in Table 3.

**Table 3: Number (%) of Patients with Adverse Reactions with  $\geq 5$  Percent Occurrence Rate by Body System and Treatment Group**

<b>Body System and Term</b>	<b>CENESTIN 0.30 mg</b>	<b>Placebo</b>
<b>Body as a Whole</b>	22 (60)	13 (38)
Allergic Reaction	3 (8)	1 (3)
Flu Syndrome	3 (8)	1 (3)
Injury Accident	2 (5)	1 (3)
Back Pain	2 (5)	1 (3)
Cyst	2 (5)	0 (0)
Asthenia	3 (8)	2 (6)
<b>Digestive</b>	10 (27)	8 (24)
Nausea	4 (11)	2 (6)
Dyspepsia	2 (5)	1 (3)
Vomiting	3 (8)	0 (0)
Increased Appetite	2 (5)	0 (0)
<b>Neurological</b>	7 (19)	7 (21)
Dizziness	3 (8)	0 (0)
<b>Urogenital</b>	22 (60)	16 (47)
Leukorrhea	12 (32)	5 (15)
Vaginitis	9 (24)	5 (15)
Urinary Incontinence	3 (8)	1 (3)
Metrorrhagia	2 (5)	0 (0)
Urinary Frequency	2 (5)	0 (0)

## 6.2 Post Marketing Experience

The following adverse reactions have been identified during post-approval use of CENESTIN. 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.

Gastrointestinal disorders: abdominal distension, nausea

Investigations: weight increased

Metabolism & Nutrition Disorders: fluid retention

Neoplasms: breast cancer

Nervous System Disorders: headache, insomnia, somnolence

Psychiatric Disorder: depression

Reproductive System and Breast Disorders: breast enlargement, breast pain, breast swelling, breast tenderness

Skin & Subcutaneous Tissue Disorders: alopecia, pruritus, pruritus generalized, rash pruritic, rash

## 7 DRUG INTERACTIONS

*In vitro* and *in vivo* studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers and inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4 such as St. John's wort (*Hypericum perforatum*) preparations, phenobarbital, carbamazepine, and rifampin may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4 such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice may increase plasma concentrations of estrogens and may result in adverse reactions.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

CENESTIN is not indicated for use in pregnancy. There are no data with the use of CENESTIN in pregnant women; however, epidemiologic studies and meta-analyses have not found an increased risk of genital and nongenital birth defects (including cardiac anomalies or limb-reduction defects) following exposure to combined hormonal contraceptives (estrogen and progestins) 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 are present in human milk and can reduce milk production in breast-feeding women. This reduction can occur at any time is less likely to occur once breast-feeding is well-established. The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for CENESTIN and any potential adverse effects on the breast-fed child from CENESTIN or the underlying maternal condition.

## 8.4 Pediatric Use

CENESTIN is not indicated 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 studies utilizing CENESTIN to determine whether those over 65 years of age differ from younger subjects in their response to CENESTIN.

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

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 (14.3)*].

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 (14.3)*].

### *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-alone or estrogen plus progestin when compared to placebo [*see Warnings and Precautions (5.3)*, and *Clinical Studies (14.4)*].

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 (14.4)*].

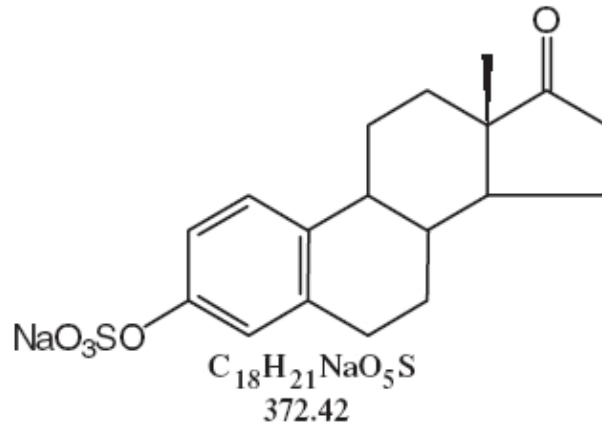
## 10 OVERDOSAGE

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

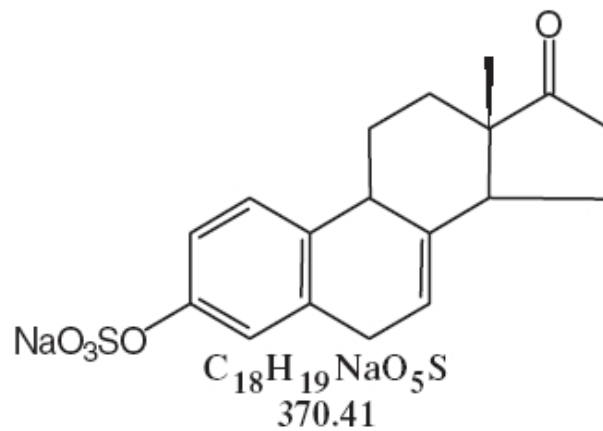
## 11 DESCRIPTION

CENESTIN (synthetic conjugated estrogens, A) tablets contain a blend of nine (9) synthetic estrogenic substances. The estrogenic substances are sodium estrone sulfate, sodium equilin sulfate, sodium 17 $\alpha$ -dihydroequilin sulfate, sodium 17 $\alpha$ -estradiol sulfate, sodium 17 $\beta$ -dihydroequilin sulfate, sodium 17 $\alpha$ -dihydroequilenin sulfate, sodium 17 $\beta$ -dihydroequilenin sulfate, sodium equilenin sulfate and sodium 17 $\beta$ -estradiol sulfate.

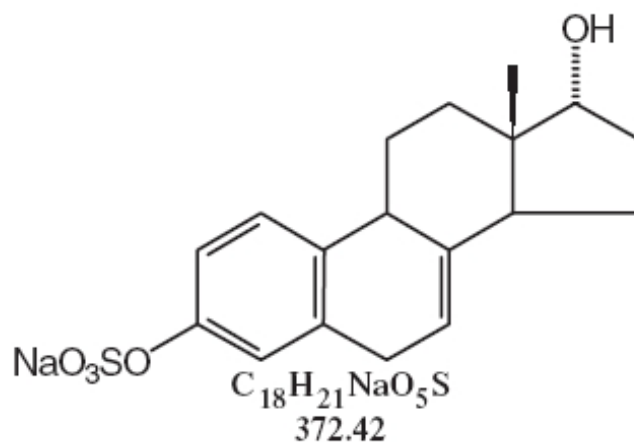
The structural formulae for these estrogens are:



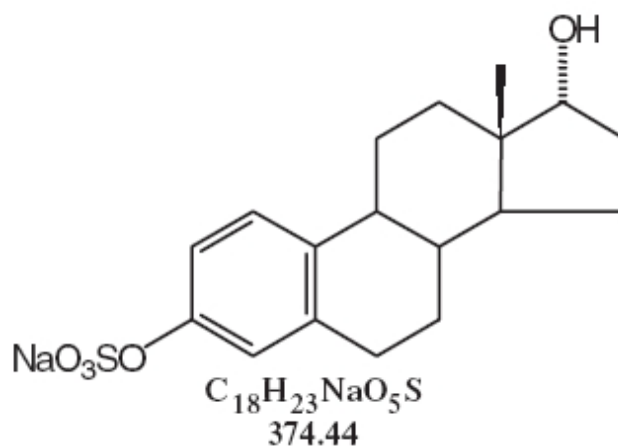
**Sodium Estrone Sulfate**



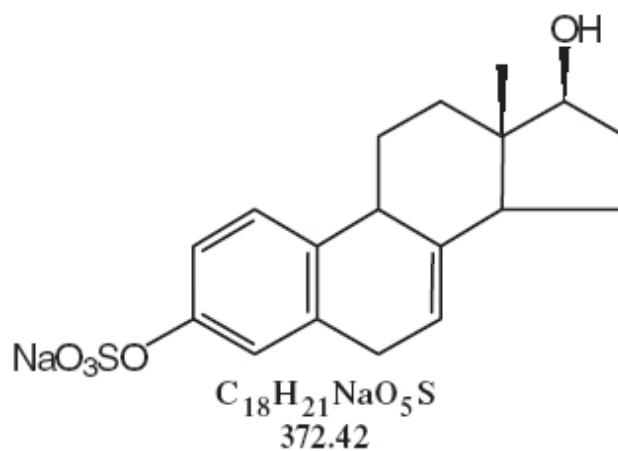
**Sodium Equilin Sulfate**



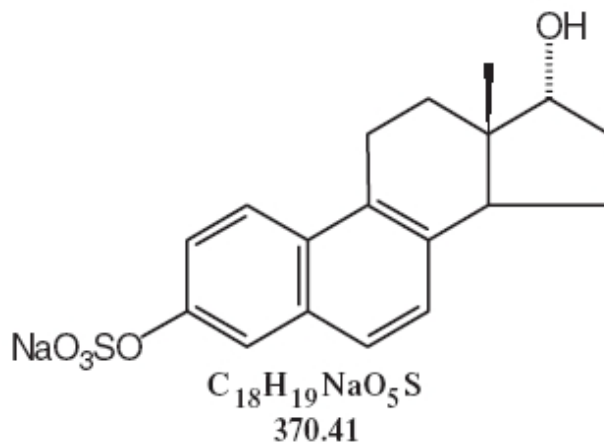
**Sodium 17 $\alpha$ -Dihydroequilin Sulfate**



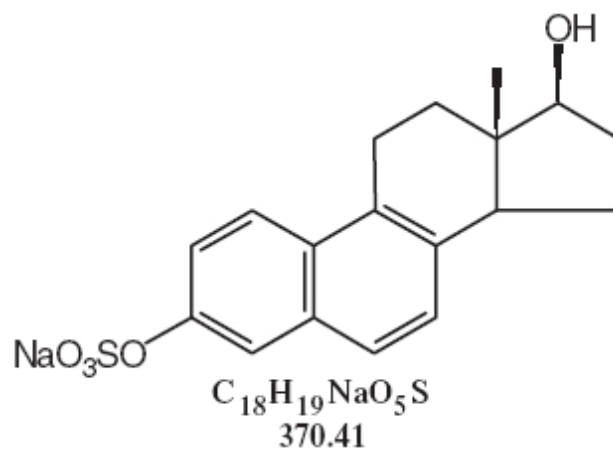
**Sodium 17 $\alpha$ -Estradiol Sulfate**



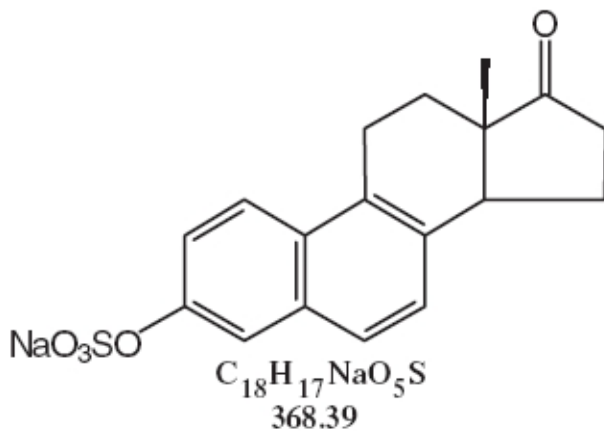
**Sodium 17 $\beta$ -Dihydroequilin Sulfate**



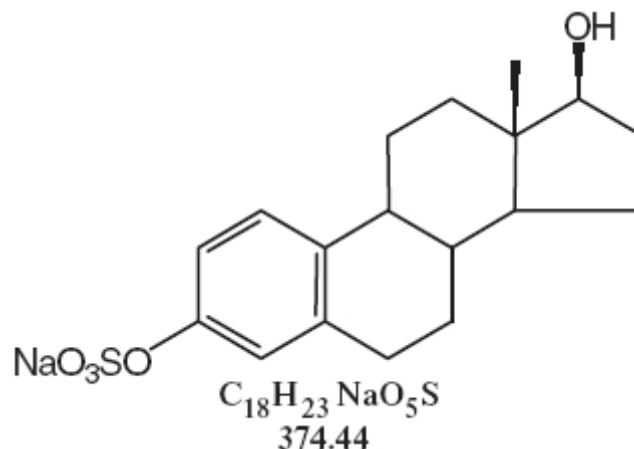
**Sodium 17 $\alpha$ -Dihydroequilenin Sulfate**



**Sodium 17 $\beta$ -Dihydroequilenin Sulfate**



**Sodium Equilenin Sulfate**



### Sodium 17β-Estradiol Sulfate

Tablets for oral administration, are available in 0.3 mg, 0.45 mg, 0.625 mg, 0.9 mg and 1.25 mg strengths of synthetic conjugated estrogens, A. Tablets also contain the following inactive ingredients: ethylcellulose, hypromellose, lactose monohydrate, magnesium stearate, polyethylene glycol, polysorbate 80 (except 0.45 mg tablets ), pregelatinized starch, titanium dioxide, and triethyl citrate.

- 0.3 mg tablets also contain FD&C Blue No. 2 aluminum lake and D&C Yellow No. 10 aluminum lake.
- 0.45 mg tablets also contain FD&C Yellow No. 6/Sunset Yellow FCF lake.
- 0.625 mg tablets also contain FD&C Red No. 40 aluminum lake.
- 0.9 mg tablets do not contain additional color additives.
- 1.25 mg tablets also contain FD&C Blue No. 2 aluminum lake.

## 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, 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.

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.

## 12.2 Pharmacodynamics

Generally, a serum estrogen concentration does not predict an individual woman's therapeutic response to CENESTIN 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.

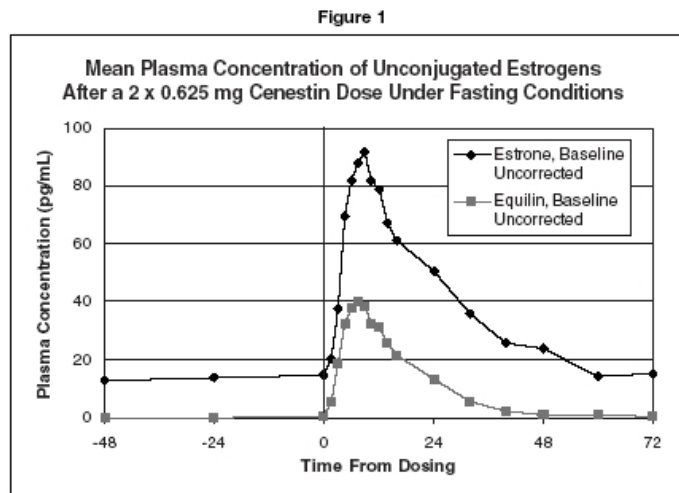
## 12.3 Pharmacokinetics

### Absorption

Synthetic conjugated estrogens, A are soluble in water and are absorbed from the gastrointestinal tract after release from the drug formulation. The effect of food on the bioavailability of synthetic conjugated estrogens, A from CENESTIN has not been studied.

**Table 4: Pharmacokinetic Parameters for Unconjugated and Conjugated Estrogens in Healthy Postmenopausal Women Under Fasting Conditions**

<b>Pharmacokinetic Parameters of Unconjugated Estrogens Following a Dose of 2 x 0.625 mg CENESTIN</b>				
Drug	Cmax (pg/mL) (CV%)	Tmax (h) (CV%)	AUC0-72h (pg•hr/mL) (CV%)	
Baseline-corrected estrone	84.5 (41.7)	8.25 (35.6)	1749 (43.8)	
Equilin	45.6 (47.3)	7.78 (28.8)	723 (67.9)	
<b>Pharmacokinetic Parameters of Conjugated Estrogens Following a Dose of 2 x 0.625 mg CENESTIN</b>				
Drug	Cmax (pg/mL) (CV%)	Tmax (h) (CV%)	t ½ (h) (CV%)	AUC0-72h (pg•hr/mL) (CV%)
Baseline-corrected estrone	4.43 (40.4)	7.7 (30.3)	10.6 (25.4)	69.89 (39.2)
Equilin	3.27 (43.5)	5.8 (31.1)	9.7 (23.0)	46.46 (47.5)



### 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 sex hormone binding globulin (SHBG) and albumin.

### 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 portion of the circulating estrogens exist as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogens.

### Excretion

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

## 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 randomized, placebo-controlled multicenter clinical study was conducted evaluating the effectiveness of CENESTIN for the treatment of moderate to severe vasomotor symptoms in 120 postmenopausal women between 38 and 66 years of age (68% were Caucasian). Patients were randomized to receive either placebo or 0.625 mg CENESTIN daily for 12 weeks. Dose titration was allowed after one week of treatment. The starting dose was either doubled (2 x 0.625 mg CENESTIN or placebo taken daily) or reduced (0.3 mg CENESTIN or placebo taken daily), if necessary. Efficacy was assessed at 4 and 12 weeks of treatment. By week 12, 10% of the study participants remained on a single 0.625 mg CENESTIN tablet daily while 77% required two (0.625 mg) tablets daily. The results in Table 5 indicate that compared to placebo, CENESTIN produced a reduction in moderate to severe vasomotor symptoms at weeks 4 and 12.

A second randomized, placebo-controlled multicenter clinical study was conducted evaluating the effectiveness of 0.45 mg CENESTIN tablets, for the treatment of moderate to severe vasomotor symptoms in 104 menopausal women between 52 and 74 years of age (76% were Caucasian). Participants were randomized to receive either placebo or 0.45 mg CENESTIN daily for 12 weeks. Efficacy was assessed at 4 and 12 weeks of treatment. The mean change in the number of moderate to severe hot flushes per week shown in Table 5 indicate that compared to placebo, 0.45 mg CENESTIN produced a reduction in moderate to severe vasomotor symptoms at weeks 4 and 12. A corresponding reduction in the severity of hot flushes was demonstrated at weeks 5 and 12.

**Table 5: Clinical Response<sup>a</sup> Mean Change in the Number of Moderate to Severe Hot Flushes per Week, 0.625 mg and 2 x 0.625 mg CENESTIN, ITT Population**

	<b>CENESTIN<sup>b</sup> 0.625 mg and 2 x 0.625 mg (n=70)</b>	<b>Placebo (n=47)</b>
Baseline		
Mean # (SD)	96.8 (42.6)	94.1 (33.9)
Week 4		
Mean # (SD)	28.7 (28.8)	45.7 (36.8)
Mean Change from Baseline (SD)	-68.1 (43.9)	-48.4 (46.2)
P-value vs. Placebo	p=.022	
Week 12		
Mean # (SD)	16.5 (25.7)	37.8 (38.7)
Mean Change from Baseline (SD)	-80.3 (50.3)	-56.3 (48.0)
P-value vs. Placebo	p=0.10	

	<b>CENESTIN<sup>b</sup> 0.625 mg and 2 x 0.625 mg (n=70)</b>	<b>Placebo (n=47)</b>
Mean = Arithmetic Mean, SD = Standard Deviation		

<sup>a</sup> Intent-to-treat population = 117

<sup>b</sup> Combined results for 0.625 mg and 0.625 mg CENESTIN tablets.

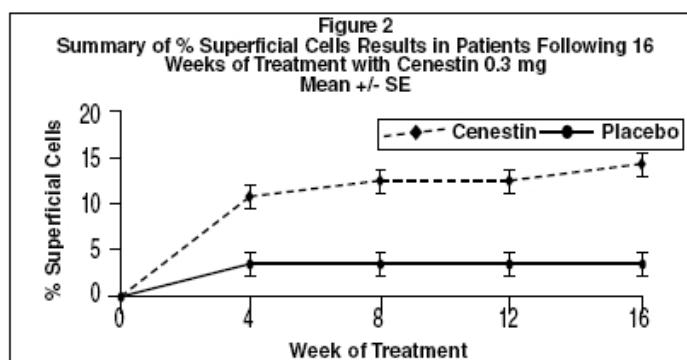
**Table 6: Clinical Response<sup>a</sup> Mean Change in the Number of Moderate to Severe Hot Flushes per Week, 0.45 mg CENESTIN, ITT Population**

	<b>CENESTIN 0.45 mg (n=53)</b>	<b>Placebo (n=51)</b>
Baseline		
Mean # (SD)	95.9 (37.0)	95.9 (41.6)
Week 4		
Mean # (SD)	45.7 (45.9)	59.4 (46.2)
Mean Change from Baseline (SD)	-50.3 (35.4)	-36.5 (42.9)
P-value vs. Placebo	p=0.14	
Week 12		
Mean # (SD)	26.1 (43.0)	50.5 (48.4)
Mean Change from Baseline (SD)	-69.9 (38.1)	-45.4 (44.7)
P-value vs. Placebo	p<.001	
Mean = Arithmetic Mean, SD = Standard Deviation		

<sup>a</sup> Intent-to-treat population = 104

## 14.2 Effects on Vulvar and Vaginal Atrophy in Postmenopausal Women

The effects of 0.3 mg CENESTIN on moderate to severe symptoms of vulvar and vaginal atrophy were confirmed in a 16-week, randomized, placebo-controlled, multicenter clinical study in 72 postmenopausal women between 30 and 77 years of age (53 percent were Caucasian). Participants were randomized to receive either placebo or 0.3 mg CENESTIN daily for 16 weeks. Efficacy was assessed at weeks 12 and 16 for vaginal wall cytology and week 16 for vaginal pH. Results for percent of superficial cells from a maturation index of the vaginal mucosa are shown in [Figure 2](#). Mean vaginal pH decreased from a baseline of 6.20 to 5.14 for CENESTIN and increased to 6.15 from a baseline of 6.03 for placebo.



### 14.3 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 either the use 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 causes. These substudies did not evaluate the effects of CE-alone or CE plus MPA on menopausal symptoms.

#### *WHI Estrogen-Alone Substudy*

The WHI estrogen-alone substudy was stopped early because an increased risk of stroke was observed, and it was deemed that no further information would be obtained regarding the risks and benefits of estrogen alone in predetermined primary endpoints. Results of the estrogen-alone substudy, which included 10,739 women (average 63 years of age, range 50 to 79; 75.3 percent White, 15.1 percent Black, 6.1 percent Hispanic, 3.6 percent Other), after an average follow-up of 7.1 years are presented in Table 7.

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

Event	Relative Risk CE vs. Placebo (95% nCI <sup>b</sup> )	CE n=5,310	Placebo n=5,429
		Absolute Risk per 10,000 Women-Years	
CHD events <sup>c</sup>	0.95 (0.78- 1.16)	54	57
<i>Nonfatal MI<sup>c</sup></i>	<i>0.91 (0.73-1.14)</i>	<i>40</i>	<i>43</i>
<i>CHD death<sup>c</sup></i>	<i>1.01(0.71- 1.43)</i>	<i>16</i>	<i>16</i>
All strokes <sup>c</sup>	1.33 (1.05-1.68)	45	33
<i>Ischemic stroke<sup>c</sup></i>	<i>1.55 (1.19-2.01)</i>	<i>38</i>	<i>25</i>

Event	Relative Risk CE vs. Placebo (95% nCI <sup>b</sup> )	CE n=5,310	Placebo n=5,429
		Absolute Risk per 10,000 Women-Years	
Deep vein thrombosis <sup>c,d</sup>	1.47 (1.06-2.06)	23	15
Pulmonary embolism <sup>c</sup>	1.37 (0.90-2.07)	14	10
Invasive breast cancer <sup>c</sup>	0.80 (0.62-1.04)	28	34
Colorectal cancer <sup>e</sup>	1.08 (0.75-1.55)	17	16
Hip fracture <sup>c</sup>	0.65 (0.45-0.94)	12	19
Vertebral fractures <sup>c,d</sup>	0.64 (0.44-0.93)	11	18
Lower arm/wrist fractures <sup>c,d</sup>	0.58 (0.47-0.72)	35	59
Total fractures <sup>c,d</sup>	0.71 (0.64-0.80)	144	197
Death due to other causes <sup>e,f</sup>	1.08 (0.88-1.32)	53	50
Overall mortality <sup>c,d</sup>	1.04 (0.88-1.22)	79	75
Global index <sup>g</sup>	1.02 (0.91-1.13)	206	201

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

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

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

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

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

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

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

For those outcomes included in the WHI “global index” that reached statistical significance, the absolute excess risk per 10,000 women-years in the group treated with CE-alone was 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 increased the risk for ischemic stroke, and this excess risk 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 [hazard ratio (HR) 0.63 (95 percent CI, 0.36-1.09)] and overall mortality [HR 0.71 (95 percent CI, 0.46-1.11)].

*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 8](#). These results reflect centrally adjudicated data after an average follow-up of 5.6 years.

**Table 8: Relative And Absolute Risk Seen in the Estrogen Plus Progestin Substudy of WHI at an Average of 5.6 Years <sup>a,b</sup>**

Event	Relative Risk CE/MPA vs. Placebo (95% nCI <sup>c</sup> )	CE/MPA n = 8,506	Placebo n = 8,102
		Absolute Risk per 10,000 Women-Years	
CHD events	1.23 (0.99-1.53)	41	34
<i>Non-fatal MI</i>	1.28 (1.00-1.63)	31	25
<i>CHD death</i>	1.10 (0.70-1.75)	8	8
All strokes	1.31 (1.03-1.68)	33	25
<i>Ischemic stroke</i>	1.44 (1.09 -1.90)	26	18
Deep vein thrombosis <sup>d</sup>	1.95 (1.43 – 2.67)	26	13
Pulmonary embolism	2.13 (1.45-3.11)	18	8

Event	Relative Risk CE/MPA vs. Placebo (95% nCI <sup>c</sup> )	CE/MPA n = 8,506	Placebo n = 8,102
		Absolute Risk per 10,000 Women-Years	
Invasive breast cancer <sup>e</sup>	1.24 (1.01-1.54)	41	33
Colorectal cancer	0.61 (0.42-0.87)	10	16
Endometrial cancer <sup>d</sup>	0.81 (0.48-1.36)	6	7
Cervical cancer <sup>d</sup>	1.44 (0.47-4.42)	2	1
Hip fracture	0.67 (0.47-0.96)	11	16
Vertebral fractures <sup>d</sup>	0.65 (0.46-0.92)	11	17
Lower arm/wrist fractures <sup>d</sup>	0.71 (0.59-0.85)	44	62
Total fractures <sup>d</sup>	0.76 (0.69-0.83)	152	199
Overall Mortality <sup>f</sup>	1.00 (0.83-1.19)	52	52
Global Index <sup>g</sup>	1.13(1.02-1.25)	184	165

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

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

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

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

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

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

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

Timing of the initiation of estrogen 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 [HR 0.69 (95 percent CI, 0.44 – 1.07)].

#### 14.4 Women’s Health Initiative Memory Study

The WHIMS estrogen-alone ancillary study of WHI enrolled 2,947 predominantly healthy postmenopausal women 65 to 79 years of age (45 percent were 65 to 69 years of age; 36 percent were 70 to 74 years of age; and 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 with 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, 0.83-2.66). 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 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 both 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 plus progestin ancillary study enrolled 4,532 predominantly healthy postmenopausal women 65 years of age and older (47 percent were 65 to 69 year 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 daily CE (0.625 mg) plus MPA (2.5 mg) on the incidence of probable dementia (primary outcome) compared with 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, 1.21-3.48) compared to placebo. 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 AD, VaD and mixed type (having features of both AD and CaD). 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, 1.19-2.60). Differences between groups became apparent in the first year of treatment. It is unknown whether these findings apply to younger postmenopausal women [see *Warnings and Precautions (5.3)*, and *Use in Specific Populations (8.5)*].

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5. 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.
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## 16 HOW SUPPLIED/STORAGE AND HANDLING

### 16.1 How Supplied

CENESTIN (synthetic conjugated estrogens, A) Tablets are available as:

0.3 mg	Round, green, film-coated, and are debossed with the letters, <b>dp</b> , on one side and the number, 41 on the other side. Available in bottles of: 100      NDC 51285-441-02
0.45 mg	Round, orange, film-coated, and are debossed with the letters, <b>dp</b> , on one side and the number, 46 on the other side. Available in bottles of: 100      NDC 51285-446-02
0.625 mg	Round, red, film-coated, and are debossed with the letters, <b>dp</b> , on one side and the number, 42 on the other side. Available in bottles of: 100      NDC 51285-442-02
0.9 mg	Round, white, film-coated, and are debossed with the letters, <b>dp</b> , on one side and the number, 43 on the other side. Available in bottles of: 100      NDC 51285-443-02
1.25 mg	Round, blue, film-coated, and are debossed with the letters, <b>dp</b> , on one side and the number, 44 on the other side. Available in bottles of: 100      NDC 51285-444-02

### 16.2 Storage and Handling

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

Dispense in tight container.

Dispense in child-resistant packaging.

Keep out of the reach of children.

Pharmacist: Include one “Information for the patient” leaflet with each package dispensed.

## **17 PATIENT COUNSELING INFORMATION**

Advise women to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

### **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-Alone Therapy**

Inform postmenopausal women of possible serious adverse reactions of estrogen-alone 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-Alone Therapy**

Inform postmenopausal women of possible less serious but common adverse reactions of estrogen-alone therapy such as headaches, breast pain and tenderness, nausea and vomiting.

Manufactured By:

Teva Women’s Health, Inc.  
Subsidiary of Teva Pharmaceuticals USA, Inc.  
North Wales, PA 19454

**Patient Information**  
**CENESTIN® (sin nes tin)**  
**(synthetic conjugated estrogens, A)**  
**Tablets**

Read this Patient Information before you start using CENESTIN and read what you get 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 medical condition or your treatment.

**What is the most important information I should know about CENESTIN (an estrogen mixture)?**

- Using estrogen-alone may increase your chance of getting cancer of the uterus (womb).
- Report any unusual vaginal bleeding right away while you are using CENESTIN. 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.
- Do not use estrogen-alone to prevent heart disease, heart attacks, strokes or dementia (decline in 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 or older.
- Do not use estrogens with progestins to prevent heart disease, heart attacks, strokes or dementia.
- Using estrogens with progestins may increase your chances of getting heart attacks, strokes, breast cancer, or blood clots.
- Using estrogens with progestins may increase your chance of getting dementia, based on a study of women 65 years of age or older.
- Only one estrogen-alone product and dose have been shown to increase your chances of getting strokes, blood clots, and dementia. Only one estrogen with progestin product and dose have been shown to increase your chances of getting heart attacks, strokes, breast cancer, 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 CENESTIN will affect your chances of these conditions. You and your healthcare provider should talk regularly about whether you still need treatment with CENESTIN.

**What is CENESTIN?**

CENESTIN is a prescription medicine that contains a mixture of estrogen hormones.

## What is CENESTIN used for?

CENESTIN is used after menopause to:

- **Reduce moderate or 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.

- **Treat moderate to severe menopausal changes in and around the vagina**

You and your healthcare provider should talk regularly about whether you still need treatment with CENESTIN to control these problems. If you use CENESTIN only to treat your menopausal changes in and around your vagina, talk with your healthcare provider about whether a topical vaginal product would be better for you.

## Who should not use CENESTIN?

### Do not start CENESTIN if you:

- **have unusual vaginal bleeding**

Vaginal bleeding after menopause may be a warning sign of cancer of the uterus (womb). Your healthcare provider should check any unusual vaginal bleeding to find out the cause.

- **have been diagnosed with a bleeding disorder**

- **currently have or have had certain cancers**

Estrogens may increase the chances 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 use CENESTIN.

- **had a stroke or heart attack**

- **currently have or have had blood clots**

- **currently have or have had liver problems**

- **are allergic to CENESTIN or any of its ingredients**

See the list of ingredients in CENESTIN at the end of this leaflet.

**Before you use CENESTIN, 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 vaginal bleeding to find out the cause.

- **have any other medical conditions that may become worse while you are using CENESTIN**

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), problems with your heart, liver, thyroid, kidneys, or have high calcium levels in your blood.

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

CENESTIN is not for pregnant women.

- **are going to have surgery or will be on bed rest**

You may need to stop using CENESTIN.

- **are breastfeeding**

The hormones in CENESTIN can pass into your breast milk.

**Tell your healthcare provider about all the medicines you take**, including prescription and non-prescription medicines, vitamins, and herbal supplements. Some medicines may affect how CENESTIN works. CENESTIN 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 new medicine.

### **How should I use CENESTIN?**

- Use CENESTIN exactly as your healthcare provider tells you to use it.
- Take 1 CENESTIN 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 using and whether you still need treatment with CENESTIN.

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

**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
- cancer of the lining of the uterus (womb)
- breast cancer

- cancer of the ovary
- dementia
- gallbladder disease
- high or low blood calcium
- visual abnormalities
- high blood pressure
- high levels of fat (triglycerides) in your blood
- liver problems
- changes in your thyroid hormone levels
- 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

**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 CENESTIN include:**

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

These are not all the possible side effects of CENESTIN. 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 Aspen Pharma USA Inc at +1-201-406-7955 or to FDA at 1-800-FDA-1088.

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

- Talk with your healthcare provider regularly about whether you should continue using CENESTIN.

- If you have a uterus, talk to your healthcare provider about whether the addition of a progestin is right for you.
- The addition of a progestin is generally recommended for a woman with a uterus to reduce the chance of getting cancer of the uterus (womb).

See your healthcare provider right away if you get vaginal bleeding while using CENESTIN.

- 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, 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 if you use tobacco, you may have higher chances of getting heart disease.

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

### **How should I store CENESTIN?**

- Store CENESTIN at room temperature between 68°F to 77°F (20°C to 25°C).

**Keep CENESTIN and all other medicines out of the reach of children.**

### **General information about safe and effective use of CENESTIN.**

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

You can ask your healthcare provider or pharmacist for information about CENESTIN that is written for health professionals. For more information call the toll-free number for Aspen Pharma USA Inc at 1-201-406-7955.

### **What are the ingredients in CENESTIN?**

**Active Ingredient:** synthetic conjugated estrogens, A

**Inactive Ingredients:** ethylcellulose, hypromellose, lactose monohydrate, magnesium stearate, polyethylene glycol, polysorbate 80 (except 0.45 mg tablets), pregelatinized starch, titanium dioxide, and triethyl citrate.

- 0.3 mg tablets also contain FD&C Blue No. 2 aluminum lake and D&C Yellow No. 10 aluminum lake.
- 0.45 mg tablets also contain FD&C Yellow No. 6/Sunset Yellow FCF lake.
- 0.625 mg tablets also contain FD&C Red No. 40 aluminum lake.
- 0.9 mg tablets do not contain any additional color additives.

- 1.25 mg tablets also contain FD&C Blue No. 2 aluminum lake.

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

Manufactured By:

**Teva Women's Health, Inc.**

Subsidiary of Teva Pharmaceuticals USA, Inc.

North Wales, PA 19454

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